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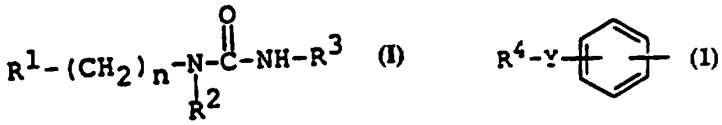
(54) Title: UREA DERIVATIVES AND THEIR USE AS ACAT-INHIBITORS

(57) Abstract

Urea derivatives of formula (I), wherein R^1 is a group of formula (1) (in which R^4 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and Y is bond, lower alkylene, -S-, -O-, (a), =CH-, -CONH-, (b), (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2NH-$, $-SO_2NHCO-$ or $-CONHSO_2-$); or thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have suitable substituent(s); R^2 is lower alkyl, lower alkoxy(lower)alkyl, cycloalkyl, ar(lower)alkyl which may have suitable substituent(s), heterocyclic group or heterocyclic(lower)alkyl, R^3 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and n is 0 or 1, and a pharmaceutically acceptable salt thereof which are useful as a medicament in the treatment of hypercholesterolemia, hyperlipidemia and atherosclerosis.



(I)

(1)

(a) (b)

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DESCRIPTION

UREA DERIVATIVES AND THEIR USEAS ACAT-INHIBITORS

TECHNICAL FIELD

This invention relates to new urea derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some urea derivatives have been known as acyl-CoA : cholesterol acyltransferase enzyme (hereinafter, ACAT) inhibitors, for example, in U.S. Patent Nos. 4,473,579 and 4,623,662, EP Patent Application Publication Nos. 0354994, 0399422 and 0512570 and PCT International Publication Nos. WO 91/13871, WO 93/24458 and WO 94/26738.

DISCLOSURE OF INVENTION

This invention relates to new urea derivatives and pharmaceutically acceptable salts thereof which have an inhibitory activity against ACAT and an advantage of good absorption into blood on oral administration, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

One object of this invention is to provide new and useful urea derivatives and pharmaceutically acceptable salts which possess an inhibitory activity against ACAT.

Another object of this invention is to provide processes for preparation of said urea derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said urea derivatives and pharmaceutically

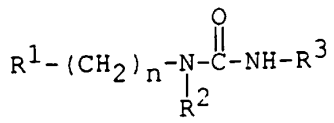
acceptable salt thereof.

Still further object of this invention is to provide a therapeutic method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby in human beings or animals, using said urea derivatives and pharmaceutically acceptable salts thereof.

High levels of blood cholesterol and blood lipids are conditions which are involved in the onset of atherosclerosis.

It is well known that inhibition of ACAT-catalyzed cholesterol esterification could lead to diminish intestinal absorption of cholesterol as well as a decrease in the intracellular accumulation of cholesterol esters in the intima of the arterial wall. Therefore, ACAT inhibitors are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis of diseases caused thereby such as cardiac insufficiency (e.g. angina pectoris, myocardial infarction, etc.), cerebrovascular disturbance (e.g. cerebral infarction, cerebral apoplexy, etc.), arterial aneurism, peripheral vascular disease, xanthomas, restenosis after percutaneous transluminal coronary angioplasty, or the like.

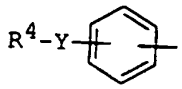
The object urea derivatives of this invention are new and can be represented by the following general formula (I):



(I)

wherein

R^1 is a group of the formula :



(in which

R^4 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and

Y is bond, lower alkylene, -S-, -O-, $-\overset{\overset{O}{\|}}{C}-$, =CH-, -CONH-, $-\underset{\underset{R^7}{|}}{N}-CO-$, (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2NH-$, $-SO_2NHCO-$ or $-CONHSO_2-$);

or

thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have suitable substituent(s);

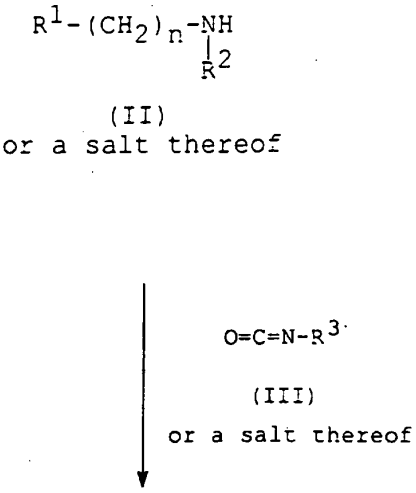
R^2 is lower alkyl, lower alkoxy(lower)alkyl, cycloalkyl, ar(lower)alkyl which may have suitable substituent(s), heterocyclic group or heterocyclic(lower)alkyl,

R^3 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and

n is 0 or 1.

The object compound (I) of the present invention can be prepared by the following processes.

Process (1)



$R^1-(CH_2)_n-NH-R^2$ (II) or a salt thereof

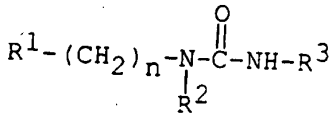
$O=C=N-R^3$ (III) or a salt thereof

$R^1-(CH_2)_n-N(R^2)-C(=O)-NH-R^3$ (I) or a salt thereof

Process (2)

$R^1-(CH_2)_n-NH-R^2$ (II) or a salt thereof + H_2N-R^3 (IV) or a salt thereof

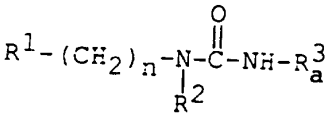
formation of ureido group



(I)

or a salt thereof

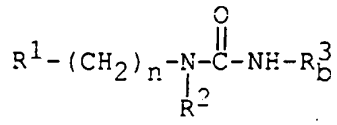
Process (3)



(Ia)

or a salt thereof

oxidation



(Ib)

or a salt thereof

wherein

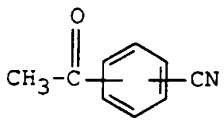
R^1, R^2, R^3 and n are each as defined above,

R_a^3 is pyridyl having two lower alkylthio and lower alkyl, and

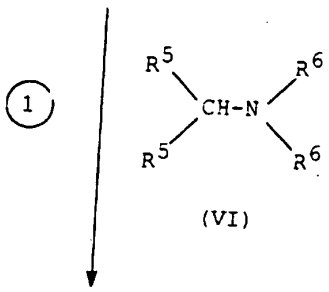
R_b^3 is pyridyl having two lower alkylsulfonyl and lower alkyl; pyridyl having two lower alkylsulfinyl and lower alkyl; or pyridyl having lower alkylsulfonyl, lower alkylsulfinyl and lower alkyl.

The starting compound can be prepared by the following processes.

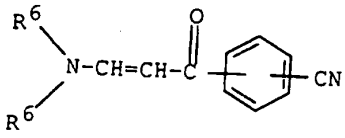
Process (A)



(V)

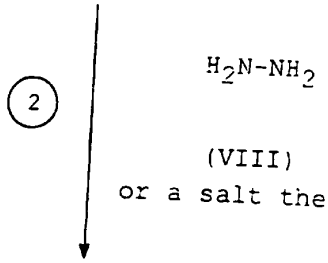


(VI)



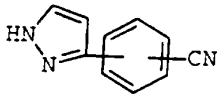
(VII)

or a salt thereof



(VIII)

or a salt thereof



(IXa)

or a salt thereof

Process (B)

R^1 - CN

(IX)

or a salt thereof

↓ reduction

R^1 - CHO

(X)

or a salt thereof

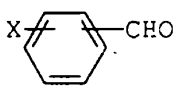
Process (C)

R^4_a - OH

(XI)

or a salt thereof

↓



(XII)

or a salt thereof

(Xa)

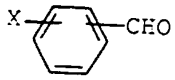
or a salt thereof

Process (D)

$R^4 - B(OH)_2$

(XIII)

or a salt thereof



(XII)

or a salt thereof

(Xb)

or a salt thereof

Process (E)

R^1 - CHO

(X)

or a salt thereof

i) R^2-NH_2

(XIV)

or a salt thereof

ii) reduction

R^1-CH_2-NH-R^2

(IIa)

or a salt thereof

wherein R^1, R^2, and R^4 are each as defined above,

R^5 is lower alkoxy,

R^6 is lower alkyl,

R^4_a is aryl which may have suitable substituent(s), and

X is a leaving group.

Suitable pharmaceutically acceptable salts of the

object compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, citrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "ar(lower)alkyl", "lower alkoxy(lower)alkyl" and "heterocyclic(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,

pentyl, tert-pentyl, hexyl, and the like, and in which more preferable example may be C_1-C_4 alkyl.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, and the like, in which more preferable example may be C_1-C_4 alkylene and the most preferable one may be methylene.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the term "lower alkoxy(lower)alkyl" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

Suitable "cycloalkyl" may include cyclo(C_3-C_7)alkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.) and the like.

Suitable "aryl" and "aryl moiety" in the term "ar(lower)alkyl" may include phenyl, naphthyl and the like.

Suitable "halogen" may include fluorine, bromine, chlorine and iodine.

Suitable "leaving group" may include acid residue, and the like.

Suitable "acid residue" may include halogen as exemplified above, and the like.

Suitable "heterocylic group" and "heterocyclic moiety" in the term "heterocyclic(lower)alkyl" may include

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 1H-1,2,4-triazolyl, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen

atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, 4H-2,3,5,6-tetrahydropyranyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 3 oxygen atom(s), for example, chromanyl, isochromanyl, methylenedioxyphenyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

Suitable "protected amino" may include acylamino or an amino group substituted by a conventional protecting group such as mono(or di or tri)aryl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.) or the like.

Suitable "hydroxy protective group" in the term "protected hydroxy" may include acyl, mono(or di or tri)phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, t-butyldimethylsilyl, etc.), etc.], substituted (lower)alkyl (e.g., methoxymethyl, ethoxymethyl, etc.), tetrahydropyranyl and the like.

Suitable "acyl" and "acyl moiety" in the term "acylamino" may include

Carbamoyl; Thiocarbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); cyclo(lower)alkylcarbonyl (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); or the like.

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like.

Suitable "substituent" in the terms "aryl which may have suitable substituent(s)" and "ar(lower)alkyl which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as exemplified above, cyclo(lower)alkyl, cyclo(lower)alkenyl, halogen as exemplified above, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl as exemplified above, ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, carboxy(lower)alkyl wherein lower alkyl moiety as exemplified above, protected carboxy(lower)alkyl, nitro, amino, protected amino, di(lower)alkylamino wherein lower alkyl moiety is as exemplified above, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected amino(lower)alkyl, hydroxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected hydroxy(lower)alkyl, cyano, sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio wherein lower alkyl moiety is as exemplified above, imino, protected amino as exemplified above, heterocyclic group which may have mono(or di or tri)ar(lower)alkyl wherein heterocyclic group, aryl moiety and lower alkyl moiety are each as exemplified above, and the like.

Suitable "substituent" in the term "heterocyclic group which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl

moiety are each as exemplified above, cyclo(lower)alkyl, cyclo(lower)alkenyl, halogen as exemplified above, carboxy, protected carboxy, hydroxy, protected hydroxy, as exemplified above, aryl as exemplified above, mono(or di or tri)ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, carboxy(lower)alkyl wherein lower alkyl moiety as exemplified above, protected carboxy(lower)alkyl, nitro, amino, protected amino, di(lower)alkylamino wherein lower alkyl moiety is as exemplified above, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected amino(lower)-alkyl, hydroxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected hydroxy(lower)alkyl, cyano, sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio wherein lower alkyl moiety is as exemplified above, lower alkylsulfinyl wherein lower alkyl moiety is as exemplified above, acyl as exemplified above, oxo, imino, and the like.

Suitable "substituent" in the term "thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl or isoxazolyl, each of which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as exemplified above, cyclo(lower)alkyl, cyclo(lower)alkenyl, halogen as exemplified above, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl as exemplified above, haloaryl wherein halogen moiety and aryl moiety are each as exemplified above, arylthio wherein aryl moiety is as exemplified above, heterocyclic group as exemplified above, ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, carboxy(lower)alkyl wherein lower alkyl moiety as exemplified above, protected carboxy(lower)alkyl, nitro, amino, protected amino, di(lower)alkylamino wherein lower alkyl moiety is as

exemplified above, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected amino(lower)alkyl, hydroxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected hydroxy(lower)alkyl, cyano, sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio wherein lower alkyl moiety is as exemplified above, imino, and the like.

The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

When the starting compound is in liquid, it can be used also as a solvent.

Process (2)

The compound (I) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof and the compound (IV) or a salt thereof to formation reaction of ureido group.

This reaction is carried out in the presence of reagent which introduces carbonyl group such as phosgene [e.g. , triphosgene, etc.], haloformate compound [e.g.

ethyl chloroformate, trichloromethyl chloroformate, phenyl chloroformate, etc.], N,N'-carbonyldiimidazole, metal carbonyl compounds [e.g. cobalt carbonyl, manganese carbonyl, etc.], a combination of carbon monoxide and catalysts such as palladium chloride, etc., or the like.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an organic base such as tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), or the like.

Process (3)

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable or oxidizing a sulfur atom to an oxidized sulfur atom, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as perbenzoic acid (e.g., perbenzoic acid, m-chloroperbenzoic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol, (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvent which does not adversely affect the

reaction.

Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (A)-(1)

The compound (VII) or a salt thereof can be prepared by reacting the compound (V) with the compound (VI).

The reaction can be carried out in the manner disclosed in Preparation 2 or similar manners thereto.

Process (A)-(2)

The compound (IXa) or a salt thereof can be prepared by reacting the compound (VII) or a salt thereof with the compound (VIII) or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 20 or similar manners thereto.

Process (B)

The compound (X) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagents to be used in chemical reduction and hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, diisobutylaluminum hydride, etc.), a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.), and the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal

platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

The reduction is usually carried out in the conventional solvent such as water, alcohol (e.g., methanol, ethanol, propanol, etc.), tetrahydrofuran, toluene, dichloromethane, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reduction is usually carried out in the presence of an organic acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

Process (C)

The compound (Xa) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the compound (XII) or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 48 or similar manners thereto.

Process (D)

The compound (Xb) or a salt thereof can be prepared by reacting the compound (XIII) or a salt thereof with the compound (XII) or a salt thereof.

The reaction can be carried out in the manner

disclosed in Preparation 38 or similar manners thereto.

Process (E)

The compound (IIa) or a salt thereof can be prepared by reacting the compound (X) or a salt thereof with the compound (XIV) or a salt thereof and then by subjecting the resultant compound to reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.) or a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, collioidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

The reduction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, propanol, etc.), tetrahydrofuran, toluene, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvents which do not adversely affect the reaction, or a

mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

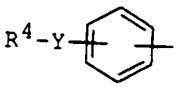
Suitable salts of the object and starting compounds in Processes (1)~(3) and (A)~(E) can be referred to the ones as exemplified for the compound (I).

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixture thereof are included within the scope of this invention.

Preferred embodiments of the object compound (I) are as follows.

R^1 is a group of the formula :



(in which

R^4 is phenyl which may have 1 to 3 suitable substituent(s) (more preferably substituent selected from the group consisting of halogen, lower alkyl, di(lower)alkylamino, protected amino (more preferably acylamino; most preferably lower alkylsulfonylamino), cyano, heterocyclic group (more preferably tetrazolyl);

which may have mono(or di or tri)ar(lower)alkyl (more preferably mono(or di or tri)phenyl(lower)alkyl; most preferably triphenyl(lower)alkyl), hydroxy, protected hydroxy (more preferably lower alkoxy(lower)alkoxy) and mono(or di or tri)halo(lower)alkyl (more preferably trihalo(lower)alkyl)), [more preferably phenyl, halophenyl, lower alkylphenyl, di(lower)alkylaminophenyl, lower alkylsulfonylaminophenyl, cyanophenyl, tetrazolylphenyl, (triphenyl(lower)-alkyltetrazolyl)phenyl, trihalo(lower)-alkylphenyl, phenyl having two lower alkyl and hydroxy, or phenyl having two lower alkyl and lower alkoxy(lower)alkoxy]; or heterocyclic group (more preferably thienyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, pyrrolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl or methylenedioxyphenyl) which may have 1 to 3 (more preferably one or two) suitable substituent(s) (more preferably substituent selected from the group consisting of lower alkyl, mono(or di or tri)ar(lower)alkyl (more preferably phenyl(lower)alkyl or triphenyl(lower alkyl) and oxo) [more preferably thienyl; pyrazolyl which may have lower alkyl or triphenyl(lower)alkyl; imidazolyl; triazolyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and phenyl(lower)alkyl; pyridyl; pyrrolyl; tetrazolyl which may have lower alkyl or triphenyl(lower)alkyl; oxazolyl; lower alkylthiazolyl; lower alkyloxadiazolyl; lower alkylpiperazinyl; dioxothiazolidinyl; or

methylenedioxyphenyl];

Y is bond, lower alkylene, -S-, -O-, -C(=O)-, =CH-, -CONH-, -N(R^7)-CO- (in which R^7 is lower alkyl), -NHSO$_2$-, -SO$_2$NH-, -SO$_2$NHCO- or -CONHSO$_2$-); or thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have 1 to 5 suitable substituent(s) (more preferably substituent selected from the group consisting of lower alkyl, hydroxy, protected hydroxy (more preferably acyloxy), phenyl, halophenyl, phenylthio and pyrrolyl) [more preferably halophenylthiazolyl, phenylimidazolyl, phenylpyrazolyl, phenylpyridyl, phenylthiopyridyl, pyrrolylpyridyl, phenylthienyl, phenylfuryl, phenylisoxazolyl or chromanyl having 4 lower alkyl and hydroxy];

R^2 is lower alkyl, lower alkoxy(lower)alkyl, cyclo(C$_3$-C$_7$)alkyl (more preferably cyclopentyl, cyclohexyl or cycloheptyl), phenyl(lower)alkyl which may have 1 to 3 (more preferably one or two; most preferably one) suitable substituent(s) (more preferably substituent(s) selected from the group consisting of halogen, lower alkoxy and di(lower alkyl)amino) [more preferably phenyl(lower)alkyl, halophenyl(lower)alkyl, lower alkoxyphenyl(lower)alkyl or di(lower alkyl)aminophenyl(lower)alkyl], tetrahydropyranyl or furyl(lower)alkyl, and

R^3 is phenyl which may have 1 to 3 (more preferably two or three) suitable substituent(s) (more preferably substituent selected from the group consisting of lower alkyl and halogen) [more preferably di(or tri)(lower alkyl)phenyl or trihalophenyl]; pyridyl or pyrimidinyl, each of which may have 1 to 3

(more preferably two or three) suitable substituent(s) (more preferably substituent selected from the group consisting of lower alkyl, lower alkylthio, halogen, lower alkoxy, lower alkylsulfinyl and lower alkylsulfonyl) [more preferably pyridyl having two lower alkylthio and lower alkyl; pyridyl having halogen, lower alkyl and lower alkylthio; tri(lower alkyl)pyridyl; pyridyl having two (lower)alkoxy and lower alkyl; pyridyl having lower alkoxy, lower alkylthio and lower alkyl; pyridyl having two lower alkylsulfinyl and lower alkyl; pyridyl having two lower alkylsulfonyl and lower alkyl; pyridyl having lower alkylthio, lower alkoxy and lower alkyl; pyridyl having lower alkylsulfinyl, lower alkylsulfonyl and lower alkyl; pyridyl having lower alkylthio, lower alkylsulfonyl and lower alkyl; pyridyl having two halogen and lower alkyl; di(lower)alkoxypyrimidinyl; or pyrimidinyl having two lower alkylthio and lower alkyl], and

n is 0 or 1.

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity against ACAT, and are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of the compound (I) are shown in the following.

Test compound (a) :

1-Cycloheptyl-1-(4-phenoxyphenylmethyl)-3-(2,4,6-trifluorophenyl)urea

Test :

Acyl-CoA : cholesterol acyltransferase (ACAT) inhibitory activity

Method :

ACAT activity was measured by the method of Heider et al. described in Journal of Lipid Research, Vol. 24, page 1127 (1983). The enzyme ACAT was prepared from the mucosal microsome fraction of the small intestine of male, 18-week old Japanese white rabbits which had been fed diet containing 2% cholesterol for 8 weeks. The inhibitory activity of test compound was calculated by measuring the amount of the labeled cholesterol ester produced from [^{14}C]oleoyl-CoA and endogenous cholesterol as follows. [^{14}C]Oleoyl-CoA and microsome were incubated with test compound at 37°C for 5 minutes. The reaction was stopped by the addition of chloroform-methanol (2:1, V/V). Cholesterol ester fraction in the chloroform-methanol extracts was isolated by thin-layer chromatography and was counted their label.

Result :

Test Compound	IC_{50} (M)
(a)	1.1×10^{-8}

For therapeutic purpose, the compound (I) of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external (topical) administration, wherein more preferable one is oral administration. The pharmaceutical preparations may

be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

- to be continued on the next page -

Preparation 1

To a solution of acetophenone (20 g) and dimethyl oxalate (23.6 g) in N,N-dimethylformamide (160 ml) was added sodium hydride (60% oil suspension, 8 g) at 0-5°C. The mixture was stirred for one hour at room temperature, then heated for 30 minutes at 50°C. After cooling, to the reaction mixture was added 2.4N-hydrochloric acid (70 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (700 g, n-hexane - ethyl acetate (4:1 to 1:1)) to give methyl 2,4-dioxo-4-phenylbutyrate (20.32 g).

IR (KBr) : 1732, 1622, 1601, 1574, 1444, 1269 cm^{-1}

NMR ($CDCl_3$, δ) : 3.95 (3H, s), 7.10 (1H, s), 7.45-7.68 (3H, m), 7.95-8.06 (2H, m), 15.0-15.5 (1H, br)

APCI-MASS (m/z) : 207 ($M+H^+$)

Preparation 2

The mixture of 3-acetylbenzonitrile (43.55 g) and N,N-dimethylformamide dimethyl acetal (107.2 g) was stirred at 90°C for 3 hours under nitrogen. The mixture was concentrated in vacuo and diisopropyl ether (400 ml) was added thereto. The red-brown precipitates were collected by filtration, washed with diisopropyl ether and dried to give 3-[(E)-3-dimethylaminopropenoyl]benzonitrile (48.62 g).

IR (KBr) : 3070, 2900, 2225, 1645, 1600, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.96 (3H, s), 3.17 (3H, s), 5.93 (1H, d, J=12.1Hz), 7.65 (1H, dd, J=7.7, 7.7Hz), 7.72 (1H, d, J=12.1Hz), 7.95 (1H, d, J=7.7Hz), 8.20 (1H, d, J=7.7Hz), 8.34 (1H, s)

APCI-MASS (m/z) : 201 ($M+H^+$)

Preparation 3

To a solution of N-(3-acetylbenzyl)-acetamide (9.56 g) in 1,2-dimethoxyethane (150 ml) was added dropwise bromine (7.99 g) at room temperature and the mixture was stirred at the same temperature for 1.5 hours. The precipitates were dissolved by addition of ethanol (150 ml) and thioacetamide (4.51 g) was added to the solution. The mixture was refluxed for 2.5 hours and evaporated in vacuo. The residue was extracted by ethyl acetate and the organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-[(2-methylthiazol-4-yl)benzyl]-acetamide (8.24 g).

IR (KBr) : 3295, 3110, 3070, 2930, 1645, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89 (3H, s), 2.72 (3H, s), 4.29 (2H, d, J=5.9Hz), 7.2-7.9 (4H, m), 7.90 (1H, s), 8.40 (1H, t, J=5.9Hz)

APCI-MASS (m/z) : 247 ($M+H^+$)

Preparation 4

To a solution of N-[3-(2-methylthiazol-4-yl)benzyl]-acetamide (8.23 g) in ethanol (100 ml) was added conc. hydrochloric acid (13.9 ml) and the mixture was refluxed for 12 hours. The mixture was cooled to 5°C and acetone (100 ml) was added thereto slowly. The precipitates were collected by filtration and washed with acetone, dried over phosphorus pentoxide to give 3-(2-methylthiazol-4-yl)-benzylamine·hydrochloride (5.14 g).

IR (KBr) : 3090, 2915, 2840, 2635, 1605, 1575, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.73 (3H, s), 4.07 (2H, ABq, J=5.7Hz), 7.47 (2H, d, J=5.1Hz), 7.9-8.0 (1H, m), 7.97 (1H, s), 8.14 (1H, s), 8.57 (2H, br s)

APCI-MASS (m/z) : 205 (M of free compound $+H^+$)

Preparation 5

To a suspension of methyl 4-[(E)-3-dimethylamino-propenoyl]benzoate (5.0 g) in methanol (150 ml) was added acetic acid (1.84 ml) and hydrazine monohydrate (1.56 ml). After stirring for 10 hours at room temperature, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give methyl 4-(pyrazol-3-yl)benzoate (4.21 g).

IR (KBr) : 2800-3500 (br), 1709, 1610, 1537, 1439, 1414 cm^{-1}

NMR (DMSO-d_6, δ) : 3.86 (3H, s), 6.85 (1H, d, J=2.2Hz), 7.84 (1H, br s), 7.85-8.10 (4H, m), 13.10 (1H, br)

APCI-MASS (m/z) : 203 ($M+H^+$)

Preparation 6

To a solution of methyl 4-[(E)-3-dimethylamino-propenoyl]benzoate (5.23 g) in acetic acid (50 ml) was added methylhydrazine (1.31 ml). The mixture was stirred for 3 hours at room temperature. To the solution was added 5N-sodium hydroxide solution in order to basify under ice cooling and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, water, brine, dried over magnesium sulfate, evaporated in vacuo. After chromatography on silica gel (eluting with dichloromethane-methanol (120:1)), methyl 4-(1-methylpyrazol-3-yl)benzoate (3.14 g) was isolated and methyl 4-(1-methylpyrazol-5-yl)benzoate (1.63 g) was obtained.

Methyl 4-(1-methylpyrazol-3-yl)benzoate:

IR (KBr) : 3134, 2949, 1705, 1612, 1439, 1344, 1281 cm^{-1}

NMR ($CDCl_3$, δ) : 3.92 (3H, s), 3.97 (3H, s), 6.61 (1H, d, J=2.2Hz), 7.41 (1H, d, J=2.2Hz), 7.82-

7.93 (2H, m), 8.03-8.14 (2H, m)
APCI-MASS (m/z) : 217 ($M+H^+$)

Methyl 4-(1-methylpyrazol-5-yl)benzoate :
IR (KBr) : 3035, 2960, 1718, 1614, 1464, 1425, 1286 cm^{-1}
NMR ($CDCl_3$, δ) : 3.93 (3H, s), 3.96 (3H, s), 6.38 (1H, d, J=2.0Hz), 7.46-7.57 (2H, m), 7.54 (1H, d, J=2.0Hz), 8.08-8.19 (2H, m)
APCI-MASS (m/z) : 217 ($M+H^+$)

Preparation 7

To a solution of thiophenol (2.20 g) in methanol (10 ml) was added 28% sodium methoxide-methanol solution (3.86 ml) and the mixture was stirred at room temperature for 15 minutes. To the mixture was added methyl 6-chloronicotinate (3.43 g) and the mixture was refluxed for 6.5 hours under nitrogen. The mixture was evaporated to dryness and the residue was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give methyl 6-(phenylthio)nicotinate (5.13 g) as a crystal.

IR (KBr) : 3070, 2950, 1720, 1585, 1550 cm^{-1}
NMR ($CDCl_3$, δ) : 3.91 (3H, s), 6.86 (1H, dd, J=8.5, 0.8Hz), 7.4-7.5 (3H, m), 7.55-7.7 (2H, m), 8.00 (1H, dd, J=8.5, 2.2Hz), 9.00 (1H, dd, J=2.2, 0.8Hz)
APCI-MASS (m/z) : 246 ($M+H^+$)

Preparation 8

To a solution of aniline (8.20 g) in pyridine (100 ml) was added portionwise 4-carboxybenzenesulfonyl chloride (17.65 g) at 5°C and the mixture was stirred at 90°C for 6

hours under nitrogen. The mixture was poured into a mixture of ethyl acetate (300 ml), ice water (200 ml) and conc. hydrochloric acid (150 ml). The precipitates were formed and collected by filtration and washed with ethyl acetate and diisopropyl ether and dried in vacuo over phosphorus pentoxide to give 4-(phenylsulfamoyl)benzoic acid (6.87 g) as white crystal. The filtrate was separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. To the residue was added diisopropyl ether and the second crop (6.57 g) was obtained by filtration.

IR (KBr) : 3265, 2840, 2675, 2560, 1680, 1600, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 7.0-7.2 (3H, m), 7.2-7.35 (2H, m), 7.85 (2H, d, J=8.4Hz), 8.07 (2H, d, J=8.4Hz), 10.45 (1H, s)

Preparation 9

To a solution of ethyl 4-aminobenzoate (8.26 g) in pyridine (25 ml) was added dropwise benzenesulfonyl chloride (8.83 g) at 5°C and the mixture was stirred at room temperature for 1 hour under nitrogen. The mixture was poured into a mixture of ethyl acetate (150 ml), ice water (100 ml) and conc. hydrochloric acid (30 ml). The precipitates were formed and collected by filtration, washed with ethyl acetate and diisopropyl ether and dried in vacuo over phosphorus pentoxide to give ethyl 4-(phenylsulfonylamino)benzoate (10.72 g) as a white crystal. The filtrate was separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. To the residue was added diisopropyl ether and the second crop (3.83 g) was obtained by filtration.

IR (KBr) : 3230, 3070, 2990, 2940, 2880, 1695, 1610, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.27 (3H, t, =7.1Hz), 4.24 (2H,

q, J=7.1Hz), 7.22 (2H, d, J=8.8Hz), 7.5-7.7 (3H, m), 7.8-7.9 (4H, m), 10.86 (1H, s)

APCI-MASS (m/z) : 306 ($M+H^+$)

Preparation 10

To a stirred mixture of bromine (50.2 ml) in dichloromethane (1 ℓ) and anhydrous sodium carbonate (206.8 g) was added a solution of 1-methylpyrazole (80 g) in dichloromethane (100 ml) at 0-5°C. After stirring for one hour under ice-cooling, the mixture was stirred for further one hour at room temperature, then cooled. To the reaction mixture water (1 ℓ) was added thereto. The dichloromethane layer was separated and aqueous layer was extracted twice with dichloromethane. The combined organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was distilled in vacuo to afford 4-bromo-1-methylpyrazole (150.6 g).

bp : 82°C (20 mmHg)

IR (Neat) : 3100, 2930 cm^{-1}

NMR ($CDCl_3$, δ) : 3.89 (3H, s), 7.38 (1H, s), 7.44 (1H, s)

APCI-MASS (m/z) : 161, 163 ($M+H^+$)

Preparation 11

To a solution of methyl 4-formylbenzoate (4.0 g) and tosylmethyl isocyanide (5.0 g) in methanol (40 ml) was added potassium carbonate (3.54 g). The mixture was refluxed for 3.5 hours. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml), washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (100 g, eluting with n-hexane - ethyl acetate (2:1 to 1:1) to give methyl 4-(oxazol-5-yl)benzoate (4.04 g).

IR (KBr) : 1726, 1614, 1275, 1109 cm^{-1}

NMR ($CDCl_3$, δ) : 3.94 (3H, s), 7.48 (1H, s), 7.68-7.78 (2H, m), 7.97 (1H, s), 8.06-8.16 (2H, m)

APCI-MASS (m/z) : 204 ($M+H^+$)

Preparation 12

A solution of methyl 2,4-dioxo-4-phenylbutyrate (6 g) and hydroxylamine·hydrochloride (6.07 g) in methanol (120 ml) was refluxed for 4 hours. The solvent was removed in vacuo. To the residue was added chloroform. The organic solution was washed with water, brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (150 g, n-hexane - ethyl acetate (3:1)) to give 3-methoxycarbonyl-5-phenylisoxazole (5.25 g).

IR (KBr) : 1728, 1570, 1448, 1250 cm^{-1}

NMR ($CDCl_3$, δ) : 4.01 (3H, s), 6.94 (1H, s), 7.45-7.55 (3H, m), 7.75-7.88 (2H, m)

APCI-MASS (m/z) : 204 ($M+H^+$)

Preparation 13

A solution of methyl 2,4-dioxo-4-phenylbutyrate (6 g) and hydrazine, monohydrate (1.42 ml) in ethanol (48 ml) was refluxed for 5 hours. The solvent was removed in vacuo. The resulting solid was collected by filtration, washed with diisopropyl ether to give 5-methoxylcarbonyl-3-pyenylpyrazole (3.0 g).

IR (KBr) : 2500-3400 (br), 1730, 1491, 1244 cm^{-1}

NMR (DMSO-d_6, δ) : 3.83, 3.88 (total 3H, each s), 7.18-7.53 (4H, m), 7.78-7.94 (2H, m), 13.90-14.15 (1H, m)

APCI-MASS (m/z) : 203 ($M+H^+$)

Preparation 14

A mixture of methyl 3-cyanobenzoate (8.0 g), sodium azide (19.38 g) and ammonium chloride (15.95 g) in N,N-dimethylformamide (32 ml) was heated for 2.5 hours at 120°C. The mixture was poured into ice water (300 ml) - ethyl acetate (100 ml). Under ice cooling, to the solution was added sodium nitrite (20.5 g) then 6N-hydrochloric acid until pH was adjusted to 1-2. After stirring for 30 minutes at room temperature, the mixture was extracted with ethyl acetate - tetrahydrofuran, washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give methyl 3-(1H-tetrazol-5-yl)benzoate (10.01 g).

IR (KBr) : 2300-3500 (br), 1705, 1684, 1618, 1562 cm^{-1}

NMR (DMSO-d_6, δ) : 3.93 (3H, s), 7.78 (1H, dd, J=7.9, 7.9Hz), 8.10-8.20 (1H, m), 8.25-8.38 (1H, m), 8.60-8.70 (1H, m)

APCI-MASS (m/z) : 205 ($M+H^+$)

Preparation 15

To the solution of 4-bromobenzyl alcohol (4.85 g) and 3-tri-n-butylstannylthiophene (11.6 g) was added tetrakis(triphenylphosphine)palladium(0) (0.9 g), then the mixture was heated for one hour at 140°C. After cooling, the resulting precipitate was collected by filtration and washed with n-hexane to give 4-(3-thienyl)benzyl alcohol (2.67 g).

IR (KBr) : 3300 (br), 1425, 1200, 1045, 1014, 777 cm^{-1}

NMR ($CDCl_3$, δ) : 1.72 (1H, t, J=5.9Hz), 4.72 (2H, d, J=5.9Hz), 7.30-7.50 (5H, m), 7.60 (2H, dd, J=6.4, 1.8Hz)

Preparation 16

The following compound was obtained according to a similar manner to that of Preparation 15.

4-(2-Thienyl)benzyl alcohol

IR (KBr) : 3300 (br), 1427, 1213, 1047, 806 cm^{-1}

NMR ($CDCl_3$, δ) : 1.70 (1H, t, J=5.9Hz), 4.71 (2H, d, J=5.9Hz), 7.08 (1H, dd, J=5.1, 3.6Hz), 7.22-7.42 (4H, m), 7.52-7.68 (2H, m)

Preparation 17

A mixture of ethyl 4-acetylbenzoate (10 g) and N,N-dimethylformamide dimethyl acetal (41.8 ml) was heated for 18 hours at 85°C. After cooling, the resulting solid was collected by filtration, washed with diisopropyl ether to give methyl 4-[(E)-3-dimethylaminopropenoyl]benzoate (10.44 g).

IR (KBr) : 1718, 1637, 1578, 1541, 1425 cm^{-1}

NMR (DMSO-d_6, δ) : 2.94 (3H, s), 3.17 (3H, s), 3.88 (3H, s), 5.85 (1H, d, J=12.2Hz), 7.77 (1H, d, J=12.2Hz), 7.90-8.05 (4H, m)

APCI-MASS (m/z) : 234 ($M+H^+$)

Preparation 18

To a suspension of lithium aluminum hydride (569 mg) in tetrahydrofuran (120 ml) was added dropwise a solution of 2-methoxycarbonyl-4-(pyrrol-1-yl)pyridine (3.03 g) at 5°C and the mixture was stirred at room temperature for 3 hours. To the mixture were added sodium fluoride (2.52 g) and water (811 mg) and the mixture was stirred at room temperature for 30 minutes. The insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give [4-(pyrrol-1-yl)pyridin-2-yl]methanol (1.14 g).

IR (KBr) : 3190, 2955, 2845, 1595, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 4.58 (2H, d, J=5.8Hz), 5.48 (1H, t, J=5.8Hz), 6.35-6.4 (2H, m), 7.52 (1H, dd, J=5.6, 2.4Hz), 6.55-6.6 (2H, m), 7.62 (1H, d, J=1.9Hz), 8.47 (1H, d, J=5.6Hz)

APCI-MASS (m/z) : 175 ($M+H^+$)

Preparation 19

The following compounds were obtained according to a similar manner to that of Preparation 18.

(1) 3-(Pyrazol-3-yl)benzyl alcohol

IR (Film) : 3245, 2930, 2880 cm^{-1}

NMR (DMSO-d_6, δ) : 4.52 (2H, d, J=5.6Hz), 5.29 (1H, t, J=5.6Hz), 6.68 (1H, d, J=2.2Hz), 7.2-7.7 (4H, m), 7.76 (1H, d, J=2.2Hz), 12.9 (1H, br s)

APCI-MASS (m/z) : 175 ($M+H^+$)

(2) (6-Phenylpyridin-3-yl)methanol

IR (Film) : 3325, 2865, 1600, 1565, 1475 cm^{-1}

NMR ($CDCl_3$, δ) : 4.74 (2H, s), 7.4-7.55 (3H, m), 7.7-7.85 (2H, m), 7.9-8.05 (2H, m), 8.62 (1H, d, J=1.3Hz)

APCI-MASS (m/z) : 186 ($M+H^+$)

(3) 4-(Benzoylamino)benzyl alcohol

IR (KBr) : 3320, 2840, 1655, 1595, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 4.50 (2H, d, J=5.7Hz), 5.22 (1H, t, J=5.7Hz), 7.05 (1H, d, J=7.6Hz), 7.29 (1H, d, J=7.6Hz), 7.5-7.7 (4H, m), 7.77 (1H, s), 7.96 (2H, dd, J=7.6, 1.5Hz), 10.23 (1H, s)

APCI-MASS (m/z) : 228 ($M+H^+$)

(4) 4-(Phenylsulfonylamino)benzyl alcohol

IR (Film) : 3515, 3265, 3060, 2935, 2875, 1705,

1650, 1615, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 4.36 (2H, d, J=5.8Hz), 5.07 (1H, t, J=5.8Hz), 7.02 (2H, d, J=8.6Hz), 7.15 (2H, d, J=8.6Hz), 7.5-7.65 (3H, m), 7.7-7.8 (2H, m), 10.21 (1H, s)

APCI-MASS (m/z) : 264 ($M+H^+$)

(5) (6-Phenylthiopyridin-3-yl)methanol

IR (Film) : 3320, 2865, 1590, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 2.46 and 2.71 (total 1H, t, J=5.6Hz), 4.64 and 4.72 (total 2H, d, J=5.6Hz), 6.88 and 7.31 (total 1H, d, J=8.3Hz), 7.4-7.75 (6H, m), 8.3-8.4 (1H, m)

APCI-MASS (m/z) : 218 ($M+H^+$)

(6) 4-(Oxazol-5-yl)benzyl alcohol

IR (KBr) : 3330 (br), 1510, 1491, 1041, 818 cm^{-1}

NMR ($CDCl_3$, δ) : 4.74 (2H, s), 7.34 (1H, s), 7.35-7.50 (2H, m), 7.59-7.72 (2H, m), 7.91 (1H, s)

APCI-MASS (m/z) : 176 ($M+H^+$)

(7) (3-Phenylpyrazol-5-yl)methanol

IR (KBr) : 2500-3500 (br), 1471, 1360, 1030, 1001, 766 cm^{-1}

NMR (DMSO-d_6, δ) : 4.38-4.58 (2H, m), 4.95-5.37 (1H, m), 6.52-6.66 (1H, m), 7.20-7.53 (3H, m), 7.68-7.90 (2H, m), 12.68-13.10 (1H, m)

APCI-MASS (m/z) : 175 ($M+H^+$)

(8) 4-(Pyrazol-3-yl)benzyl alcohol

IR (KBr) : 2500-3600 (br), 1522, 1456, 1419, 1032, 841, 762 cm^{-1}

NMR (DMSO-d_6, δ) : 4.51 (2H, d, J=5.7Hz), 5.07-5.27 (1H, m), 6.60-6.74 (1H, br s), 7.20-7.85 (5H, m),

12.82, 13.24 (total 1H, each br s)
APCI-MASS (m/z) : 175 ($M+H^+$)

(9) 4-(1-Methylpyrazol-5-yl)benzyl alcohol
IR (KBr) : 2500-3600 (br), 1495, 1460, 1425, 1385, 1273 cm^{-1}
NMR ($CDCl_3$, δ) : 2.12 (1H, t, J=5.7Hz), 3.88 (3H, s), 4.77 (2H, d, J=5.7Hz), 6.30 (1H, d, J=1.9Hz), 7.35-7.52 (4H, m), 7.51 (1H, d, J=1.9Hz)
APCI-MASS (m/z) : 189 ($M+H^+$)

(10) 3-(1H-Tetrazol-5-yl)benzoyl alcohol
IR (KBr) : 2100-3600 (br), 1562, 1485, 1419, 1219 cm^{-1}
NMR (DMSO-d_6, δ) : 4.61 (2H, s), 5.20-5.60 (1H, br), 7.48-7.65 (2H, m), 7.85-7.98 (1H, m), 8.05 (1H, s)
APCI-MASS (m/z) : 177 ($M+H^+$)

Preparation 20

To a solution of 3-[(E)-3-dimethylaminopropenoyl]-benzonitrile (48.5 g) in methanol (500 ml) was added acetic acid (21.82 g) followed by slow addition of hydrazine monohydrate (18.17 g) at room temperature and the mixture was stirred at 17.5 hours at the same temperature. The mixture was evaporated to dryness and the residue was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized and the crystal was collected by filtration, washed with diisopropyl ether and dried to give 3-(pyrazol-3-yl)benzonitrile (37.71 g).

IR (KBr) : 3190, 3075, 2840, 2760, 2230, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 6.88 (1H, d, J=2.1Hz), 7.62 (1H, dd, J=7.7, 7.7Hz), 7.75 (1H, d, J=7.7Hz), 7.83

(1H, br s), 8.16 (1H, d, J=7.7Hz), 8.24 (1H, s), 13.08 (1H, br)

Preparation 21

To a suspension of sodium hydride (2.0 g) in N,N-dimethylformamide (100 ml) was added thiophenol (5.51 g), and the mixture was stirred at room temperature for 15 minutes. To the mixture was added 4-fluorobenzonitrile (6.66 g), and the mixture was stirred at 130°C for 16 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(phenylthio)benzonitrile (12.24 g) as an oil.

IR (Film) : 3070, 2235, 1595, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 7.15-7.3 (2H, m), 7.65-7.8 (2H, m), 7.4-7.6 (5H, m)

APCI-MASS (m/z) : 212 ($M+H^+$)

Preparation 22

To a suspension of 4-(phenylsulfamoyl)benzoic acid (13.43 g) in 1,2-dichloroethane (130 ml) were added thionyl chloride (11.52 g) and N,N-dimethylformamide (2 drops) and the mixture was stirred at 100°C for 2 hours, under nitrogen. The resulting solution was evaporated in vacuo and the residue was dissolved in dichloromethane (150 ml). To this solution was added N,O-dimethylhydroxylamine·hydrochloride (5.19 g), followed by dropwise addition of triethylamine (9.80 g) at 5°C. The mixture was stirred at room temperature for 4 hours. Water was added thereto and the separated organic layer was washed with brine, dried over magnesium sulfate and evaported in vacuo. The residue was purified by column chromatography on silica gel to give N-methyl-N-methoxy-4-(phenylsulfamoyl)benzamide (11.31 g)

as an oil.

IR (KBr) : 3150, 2950, 2905, 2890, 1625, 1600, 1570, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 3.24 (3H, s), 3.48 (3H, s), 7.0-7.2 (3H, m), 7.2-7.3 (2H, m), 7.7-7.9 (4H, m), 10.38 (1H, s)

Preparation 23

To the solution of 4-fluorobenzonitrile (10 g) and pyrazole (6.74 g) in N,N-dimethylformamide (100 ml) was added potassium carbonate (13.7 g). Then the mixture was heated for 4 hours at 120°C. After cooling, the reaction mixture was diluted with ethyl acetate (1 ℓ), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (400 g, eluting with n-hexane - ethyl acetate (3:1)) to give 4-(pyrazol-1-yl)benzonitrile (10.54 g).

IR (KBr) : 2226, 1608, 1529, 1394 cm^{-1}

NMR ($CDCl_3$, δ) : 6.54 (1H, dd, J=2.5, 1.8Hz), 7.70-7.90 (5H, m), 8.00 (1H, d, J=2.5Hz)

APCI-MASS (m/z) : 170 ($M+H^+$)

Preparation 24

To the solution of 4-fluorobenzonitrile (10 g) and imidazole (6.74 g) in N,N-dimethylformamide (200 ml) was added potassium carbonate (13.7 g). Then the mixture was heated for 2 hours at 120°C. After cooling, the reaction mixture was diluted with ethyl acetate (2 ℓ), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo to give 4-(imidazol-1-yl)benzonitrile (10.34 g).

IR (KBr) : 2225, 1608, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 7.27 (1H, s), 7.34 (1H, t, J=1.2Hz), 7.46-7.60 (2H, m), 7.75-7.89 (2H, m), 7.95 (1H, s)

APCI-MASS (m/z) : 170 ($M+H^+$)

Preparation 25

To a solution of methyl 4-(1-methylpyrazol-3-yl)benzoate (2.5 g) in dichloromethane (80 ml) was added dropwise diisobutylaluminum hydride (1.02M toluene solution, 25.0 ml) at -60 - -50°C. After stirring for 30 minutes at the same temperature, sodium fluoride (4.28 g) and water (1.38 ml) was added thereto. The mixture was warmed to room temperature over 15 minutes and stirred for one hour. Insoluble materials were removed by filtration. The filtrate was evaporated in vacuo to give 4-(1-methylpyrazol-3-yl)benzyl alcohol (1.74 g).

IR (KBr) : 2500-3650 (br), 1508, 1462, 1431, 1360, 1302 cm^{-1}

NMR ($CDCl_3$, δ) : 1.90 (1H, t, J=5.7Hz), 3.95 (3H, s), 4.70 (2H, d, J=5.7Hz), 6.54 (1H, d, J=2.2Hz), 7.33-7.43 (3H, m), 7.74-7.84 (2H, m)

APCI-MASS (m/z) : 189 ($M+H^+$)

Preparation 26

To a solution of 4-bromo-1-methylpyrazole (1 g) in ether (15 ml) was added dropwise n-butyllithium (1.63M in hexane, 4.2 ml) keeping the temperature below -60°C. After stirring for 30 minutes, a solution of tri-n-butyltin chloride (1.85 ml) in ether (1.85 ml) was added thereto. After stirring for one hour, the mixture was warmed to room temperature over 30 minutes and stirred for one hour. The reaction mixture was diluted with ether, washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 1-methyl-4-tri-(n-butyl)stannylpyrazole (2.3 g).

IR (Neat) : 2930, 1504, 1460, 1120 cm^{-1}

NMR ($CDCl_3$, δ) : 0.75-1.70 (27H, m), 3.93 (3H, s), 7.23 (1H, s), 7.42 (1H, s)

Preparation 27

To a suspension of 5-bromo-2-furancarboxylic acid (10 g), N,O-dimethylhydroxylamine·hydrochloride (5.1 g) and 1-hydroxybenzotriazole (7.07 g) in dichloromethane (300 ml) was added dropwise a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (6.37 g) in dichloromethane (60 ml) at room temperature. The resulting mixture was stirred at room temperature for 18 hours. Water (180 ml) was added thereto and the insoluble materials were removed by filtration. The organic layer was separated and washed with brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (350 g, eluting with ethyl acetate - n-hexane (1:1)) to give 5-bromo-2-(N-methyl-N-methoxycarbamoyl)furan (7.60 g).

IR (Neat) : 2974, 2937, 1649, 1566, 1477 cm^{-1}

NMR ($CDCl_3$, δ) : 3.34 (3H, s), 3.77 (3H, s), 6.45 (1H, d, J=3.5Hz), 7.09 (1H, d, J=3.5Hz)

APCI-MASS (m/z) : 234, 236 ($M+H^+$)

Preparation 28

To a mixture of 3-methylbiphenyl (5.0 g) and N-bromosuccinimide (5.29 g) in tetrachloromethane (150 ml) was added benzoyl peroxide (144 mg) and the mixture was refluxed for 6 hours. The mixture was cooled, and the insoluble materials were filtered off. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give crude 3-bromomethyl biphenyl (6.59 g) as a yellow oil.

IR (Film) : 3030, 1600, 1575 cm^{-1}

NMR ($CDCl_3$, δ) : 4.56 (2H, s), 7.35-7.7 (9H, m)

Preparation 29

The following compounds were obtained according to a similar manner to that of Preparation 28.

(1) 4-Bromomethylbenzophenone

IR (KBr) : 3050, 1650, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 4.54 (2H, s), 7.4-7.85 (9H, m)

(2) 4-(Pyridin-3-yl)benzyl bromide

NMR (DMSO-d_6, δ) : 6.10 (2H, s), 7.4-8.4 (6H, m), 8.9-9.3 (2H, m)

(3) 4-(Pyridin-2-yl)benzyl bromide

IR (Film) : 3050, 3010, 2985, 1735, 1585, 1565 cm^{-1}

NMR ($CDCl_3$, δ) : 4.58 (2H, s), 7.2-8.1 (7H, m), 8.7-8.8 (1H, m)

Preparation 30

To a solution of 4-ethoxycarbonyl-2-(4-chlorophenyl)thiazole (2.68 g) in a mixture of tetrahydrofuran (40 ml) and ethanol (10 ml) was added lithium borohydride (218 mg) at room temperature and the mixture was stired at 50°C for 1.5 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue crystalline solid was collected by filtration to give [2-(4-chlorophenyl)thiazol-4-yl]methanol (1.43 g).

IR (KBr) : 3270, 3080, 2920, 2865, 1595, 1525, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 4.63 (2H, d, J=5.8Hz), 5.40 (1H, t, J=5.8Hz), 7.51 (1H, s), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

APCI-MASS (m/z) : 226 ($M+H^+$)

Preparation 31

To a solution of methyl 6-chloronicotinate (6.86 g) and dihydroxyphenyl borane (5.85 g) in 1,2-dimethoxyethane

(150 ml) was added 2M sodium carbonate aqueous solution (48 ml), followed by tetrakis(triphenylphosphine)palladium(0) (2.31 g) and the mixture was refluxed for 16 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give methyl 6-phenylnicotinate (7.75 g) as a white crystal.

IR (KBr) : 3070, 3030, 2995, 2945, 2845, 1725, 1595, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 3.98 (3H, s), 7.4-7.6 (3H, m), 7.82 (1H, dd, J=8.3, 0.9Hz), 8.0-8.1 (2H, m), 8.35 (1H, dd, J=8.3, 2.2Hz), 9.28 (1H, dd, J=2.2, 0.9Hz)

Preparation 32

The following compound was obtained according to a similar manner to that of Preparation 31.

N-Methyl-N-methoxy-4-[4-(dimethylamino)phenyl]-benzamide

IR (KBr) : 3255, 3000, 2815, 1605, 1540, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 3.01 (6H, s), 3.38 (3H, s), 3.60 (3H, s), 6.80 (2H, d, J=8.9Hz), 7.5-7.65 (4H, m), 7.74 (2H, dd, J=6.5, 1.9Hz)

APCI-MASS (m/z) : 285 ($M+H^+$)

Preparation 33

To a suspension of 4-(pyrrol-1-yl)benzoic acid (3.74 g) and N,O-dimethylhydroxylamine·hydrochloride (1.95 g) in dichloromethane (100 ml) was added dropwise a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.43 g) in dichloromethane (15 ml) at room temperature. The resulting solution was stirred at the same temperature for 18 hours.

Water (60 ml) was added to the mixture, and the insoluble materials were removed by filtration. The filtrate was separated, and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(pyrrol-1-yl)-N-methyl-N-methoxybenzamide (2.12 g) as a white crystal.

IR (KBr) : 3130, 3045, 2975, 2935, 1640, 1610, 1580, 1525 cm^{-1}

NMR ($CDCl_3$, δ) : 3.39 (3H, s), 3.58 (3H, s), 6.4-6.45 (2H, m), 7.15-7.2 (2H, m), 7.4-7.5 (2H, m), 7.8-7.9 (2H, m)

APCI-MASS (m/z) : 231 ($M+H^+$)

Preparation 34

To a suspension of 3-(pyrrol-1-yl)benzoic acid (5.62 g), N,O-dimethylhydroxylamine·hydrochloride (2.93 g) and 1-hydroxybenzotriazole (4.05 g) in dichloromethane (150 ml) was added dropwise a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (3.65 g) in dichloromethane (30 ml) at room temperature. The resulting solution was stirred at room temperature for 20 hours. Water (100 ml) was added thereto and the insoluble materials were removed by filtration. The filtrate was separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(pyrrol-1-yl)-N-methyl-N-methoxybenzamide (5.19 g) as a yellow oil.

IR (Film) : 3130, 2935, 1645, 1610, 1585, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 3.39 (3H, s), 3.57 (3H, s), 6.35-6.4 (2H, m), 7.1-7.15 (2H, m), 7.45-7.6 (3H, m), 8.7-8.75 (1H, m)

APCI-MASS (m/z) : 231 ($M+H^+$)

Preparation 35

The following compound was obtained according to a similar manner to that of Preparation 34.

[4-(N-Methyl-N-methoxy)carbamoylphenyl]-dihydroxyborane

IR (KBr) : 3380, 1610, 1545, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.53 (3H, s), 7.5-7.8 (4H, m)

APCI-MASS (m/z) : 210 ($M+H^+$)

Preparation 36

To a suspension of lithium aluminum hydride (348 mg) in tetrahydrofuran (30 ml) was added dropwise a solution of 4-(pyrrol-1-yl)-N-methyl-N-methoxybenzamide (2.11 g) in tetrahydrofuran (40 ml) at 5°C and the mixture was stirred at 5°C for 1.5 hours. To the mixture were added sodium fluoride (1.54 g) and water (495 mg), and the mixture was stirred at room temperature for 30 minutes. The insoluble materials were filtered off and washed with tetrahydrofuran. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 4-(pyrrol-1-yl)benzaldehyde (1.65 g).

IR (KBr) : 3130, 2800, 2745, 1690, 1605, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 6.35-6.45 (2H, m), 7.15-7.25 (2H, m), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m), 9.99 (1H, s)

APCI-MASS (m/z) : 172 ($M+H^+$)

Preparation 37

The following compounds were obtained according to a similar manner to that of Preparation 36.

(1) 3-(Pyrrol-1-yl)benzaldehyde

IR (Film) : 3220, 1700, 1650, 1590, 1540, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 6.4-6.45 (2H, m), 7.15-7.20 (2H, m), 7.55-7.8 (3H, m), 8.9-8.95 (1H, m), 10.06 (1H, s)

APCI-MASS (m/z) : 172 ($M+H^+$)

(2) 4-(4-Dimethylaminophenyl)benzaldehyde

IR (KBr) : 2895, 2810, 2725, 1695, 1680, 1595, 1540 cm^{-1}

NMR ($CDCl_3$, δ) : 3.03 (6H, s), 6.8-6.9 (2H, m), 7.55-7.65 (2H, m), 7.65-7.75 (2H, m), 7.85-7.95 (2H, m), 10.01 (1H, s)

APCI-MASS (m/z) : 226 ($M+H^+$)

(3) 4-(Phenylsulfamoyl)benzaldehyde

IR (KBr) : 3260, 3055, 2860, 1695, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 7.0-7.15 (3H, m), 7.2-7.3 (2H, m), 7.93 (2H, d, J=8.1Hz), 8.05 (2H, d, J=8.1Hz), 10.04 (1H, s), 10.48 (1H, br s)

APCI-MASS (m/z) : 262 ($M+H^+$)

(4) 2-Bromo-5-furaldehyde

IR (KBr) : 1670, 1464, 1377, 1271 cm^{-1}

NMR ($CDCl_3$, δ) : 6.57 (1H, d, J=3.6Hz), 7.19 (1H, d, J=3.6Hz), 9.54 (1H, s)

Preparation 38

To a suspension of 4-bromobenzaldehyde (1.85 g) and [4-flurophenyl]dihydroxyborane (1.40 g) in toluene (50 ml) was added powdered potassium carbonate (2.07 g), followed by addition of tetrakis(triphenylphosphine)palladium(0) (578 mg) and the mixture was refluxed for 24 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by

column chromatography on silica gel to give 4-(4-fluorophenyl)benzaldehyde (1.67 g) as a white crystal.

IR (KBr) : 3055, 2855, 2755, 1705, 1600, 1565, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 7.1-7.25 (2H, m), 7.55-7.7 (2H, m), 7.71 (2H, d, J=8.2Hz), 7.95 (2H, d, J=8.2Hz), 10.06 (1H, s)

APCI-MASS (m/z) : 201 ($M+H^+$)

Preparation 39

To a solution of 2-bromo-5-thiophenecarbaldehyde (2 g) and dihydroxyphenylborane (1.66 g) was added 2M sodium carbonate solution (13.6 ml) and tetrakis(triphenylphosphine)palladium(0) (605 mg). The mixture was heated for 5 hours at 80°C. The reaction mixture was poured into water, extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (100 g, eluting with n-hexane - ethyl acetate (5:1)) to give 2-phenyl-5-thiophenecarbaldehyde (1.80 g).

IR (KBr) : 1647, 1441, 1232, 754 cm^{-1}

NMR ($CDCl_3$, δ) : 7.33-7.50 (4H, m), 7.60-7.80 (3H, m), 9.90 (1H, s)

APCI-MASS (m/z) : 189 ($M+H^+$)

Preparation 40

The following compounds were obtained according to a similar manner to that of Preparation 39.

(1) 2-Phenyl-5-furaldehyde

IR (Neat) : 1674, 1522, 1475, 1257 cm^{-1}

NMR ($CDCl_3$, δ) : 6.85 (1H, d, J=3.7Hz), 7.33 (1H, d, J=3.7Hz), 7.37-7.53 (3H, m), 7.80-7.92 (2H, m), 9.66 (1H, s)

APCI-MASS (m/z) : 173 ($M+H^+$)

(2) 4-Phenyl-2-thiophenecarbaldehyde

IR (KBr) : 1676, 1539, 1429, 1173, 760 cm^{-1}

NMR ($CDCl_3$, δ) : 7.30-7.66 (5H, m), 7.82-7.90 (1H, m), 8.00-8.08 (1H, m), 9.98 (1H, d, J=1.2Hz)

FAB-MASS (m/z) : 189 ($M+H^+$)

(3) 4-(4-Methylphenyl)benzaldehyde

IR (KBr) : 3095, 3060, 2860, 2765, 1690, 1600, 1575, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 7.29 (2H, d, J=10.4Hz), 7.55 (2H, dd, J=6.3, 1.8Hz), 7.74 (2H, dd, J=6.6, 1.8Hz), 7.94 (2H, dd, J=6.6, 1.8Hz), 10.05 (1H, s)

APCI-MASS (m/z) : 197 ($M+H^+$)

(4) 4-(4-Chlorophenyl)benzaldehyde

IR (KBr) : 3055, 2820, 2720, 1695, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 7.4-7.5 (2H, m), 7.55-7.65 (2H, m), 7.7-7.8 (2H, m), 7.9-8.0 (2H, m), 10.06 (1H, s)

APCI-MASS (m/z) : 217 ($M+H^+$)

(5) 4-(4-Bromophenyl)benzaldehyde

IR (KBr) : 3050, 2820, 2725, 1705, 1605, 1575, 1555 cm^{-1}

NMR ($CDCl_3$, δ) : 7.45-7.55 (2H, m), 7.55-7.65 (2H, m), 7.65-7.75 (2H, m), 7.95-8.05 (2H, m), 10.06 (1H, s)

APCI-MASS (m/z) : 263, 261 ($M+H^+$)

Preparation 41

To a solution of 4-carboxybenzaldehyde (3.00 g) and triethylamine (2.23 g) in dichloromethane (50 ml) was added

dropwise isobutyl chloroformate (3.01 g) at 5°C and the mixture was stirred at 5°C for 40 minutes. To this solution was added aniline (2.05 g) and the mixture was stirred at room temperature for 16 hours. Water was added to the mixture, and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. To the residue was added hexane:ethyl acetate (1:1) and the powder was collected by filtration to give 4-(phenylcarbamoyl)benzaldehyde (2.24 g). The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give the second crop (1.12 g).

IR (KBr) : 3340, 3055, 2820, 2725, 1705, 1650, 1575, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 7.13 (1H, t, J=7.3Hz), 7.3-7.45 (2H, m), 7.79 (2H, d, J=7.5Hz), 8.0-8.2 (4H, m), 10.12 (1H, s), 10.46 (1H, s)

APCI-MASS (m/z) : 226 ($M+H^+$)

Preparation 42

To a solution of ethyl 4-aminobenzoate (3.30 g) in pyridine (10 ml) was added dropwise benzoyl chloride (3.09 g) at 5°C, and the mixture was stirred at room temperature for 1.6 hours. The mixture was poured into a mixture of ethyl acetate, ice water and 6N hydrochloric acid (40 ml), and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from hexane and ethyl acetate (5:1), and the crystal was collected by filtration to give ethyl 4-(benzoylamino)-benzoate (5.14 g).

IR (KBr) : 3300, 3050, 2980, 1720, 1650, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.34 (3H, t, J=7.1Hz), 4.34 (2H, q, J=7.1Hz), 7.5-7.7 (5H, m), 7.95-8.2 (3H, m), 8.45-8.5 (1H, m), 10.48 (1H, s)

APCI-MASS (m/z) : 270 ($M+H^+$)

Preparation 43

The following compound was obtained according to a similar manner to that of Preparation 41.

4-(2-Pyridylcarbamoyl)benzaldehyde

IR (KBr) : 3230, 3180, 3115, 3035, 2810, 2725, 1710, 1675, 1585, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 7.20 (1H, dd, J=6.8, 1.5Hz), 7.8-7.9 (1H, m), 8.03 (2H, d, J=8.4Hz), 8.20 (2H, d, J=8.4Hz), 8.15-8.25 (1H, m), 8.4-8.45 (1H, m), 10.12 (1H, s), 11.06 (1H, s)

APCI-MASS (m/z) : 227 ($M+H^+$)

Preparation 44

To a solution of [2-(4-chlorophenyl)thiazol-4-yl]methanol (1.42 g) in chloroform (80 ml) was added activated manganese dioxide (5.48 g) and the mixture was refluxed for 1.8 hours. The mixture was filtered and the filtrate was evaporated in vacuo to give 4-formyl-2-(4-chlorophenyl)thiazole (1.28 g).

IR (KBr) : 3110, 2840, 1695, 1595, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 7.55-7.65 (2H, m), 8.0-8.1 (2H, m), 8.80 (1H, s), 9.99 (1H, s)

APCI-MASS (m/z) : 224 ($M+H^+$)

Preparation 45

To a solution of (3-phenylpyrazol-5-yl)methanol (1.30 g) in acetone (130 ml) was added activated manganese dioxide (6.5 g) and the mixture was refluxed 1.5 hours. The mixture was filtered and the filtrate was evaporated in vacuo to give 3-phenyl-5-formylpyrazole (1.16 g).

IR (KBr) : 2400-3500 (br), 1676, 1473, 1282, 1192 cm^{-1}

NMR (DMSO-d_6, δ) : 7.20-7.56 (4H, m), 7.75-7.95 (2H, m), 9.93 (1H, s), 14.05-14.30 (1H, br)
APCI-MASS (m/z) : 173 ($M+H^+$)

Preparation 46

The following compounds were obtained according to similar manners to those of Preparations 44 and 45.

(1) 3-(Pyrazol-3-yl)benzaldehyde
IR (Film) : 3325, 2975, 2920, 2840, 2745, 1700, 1610, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 6.84 (1H, d, J=2.0Hz), 7.6-8.25 (4H, m), 8.36 (1H, s), 10.07 (1H, s), 13.05 (1H, br s)
APCI-MASS (m/z) : 173 ($M+H^+$)

(2) 6-Phenyl-3-formylpyridine
IR (KBr) : 3060, 2835, 2785, 2740, 1695, 1590, 1560 cm^{-1}
NMR ($CDCl_3$, δ) : 7.25-7.4 (4H, m), 7.92 (1H, d, J=8.3Hz), 8.05-8.15 (2H, m), 8.24 (1H, dd, J=8.3, 2.2Hz), 9.14 (1H, dd, J=2.2, 0.7Hz), 10.14 (1H, s)
APCI-MASS (m/z) : 184 ($M+H^+$)

(3) 2-Formyl-4-(pyrrol-1-yl)pyridine
IR (KBr) : 3110, 2845, 1705, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 6.35-6.4 (2H, m), 7.75-7.8 (2H, m), 7.98 (1H, dd, J=5.2, 2.5Hz), 8.12 (1H, d, J=2.2Hz), 8.80 (1H, d, J=5.5Hz), 10.0 (1H, s)
APCI-MASS (m/z) : 173 ($M+H^+$)

(4) 6-Phenylthio-3-formylpyridine
IR (Film) : 3055, 2840, 2780, 1700, 1585, 1550 cm^{-1}
NMR ($CDCl_3$, δ) : 6.94 and 7.49 (total 1H, d,

J=8.4Hz), 7.45-7.65 (6H, m), 7.89 and 8.14 (total 1H, dd, J=8.4, 2.2Hz), 8.82 and 8.87 (total 1H, d, J=2.2Hz), 9.98 and 10.10 (total 1H, s)
APCI-MASS (m/z) : 216 ($M+H^+$)

(5) 4-(Benzoylamino)benzaldehyde
IR (KBr) : 3305, 3055, 2840, 2735, 1715, 1660, 1645, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 7.5-7.7 (5H, m), 7.95-8.15 (3H, m), 8.40 (1H, s), 10.02 (1H, s), 10.54 (1H, s)
APCI-MASS (m/z) : 226 ($M+H^+$)

(6) 4-(Phenylsulfonylamino)benzaldehyde
IR (KBr) : 3240, 3060, 2935, 2850, 2765, 1690, 1680, 1580, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 7.29 (2H, d, J=8.6Hz), 7.55-7.7 (3H, m), 7.75-7.9 (4H, m), 9.81 (1H, s), 11.01 (1H, s)
APCI-MASS (m/z) : 262 ($M+H^+$)

(7) 4-(3-Thienyl)benzaldehyde
IR (KBr) : 1689, 1601, 1211, 1167 cm^{-1}
NMR ($CDCl_3$, δ) : 7.41-7.47 (2H, m), 7.62 (1H, t, J=2.1Hz), 7.70-7.83 (2H, m), 7.85-7.98 (2H, m), 10.02 (1H, s)
APCI-MASS (m/z) : 189 ($M+H^+$)

(8) 4-(2-Thienyl)benzaldehyde
IR (KBr) : 1699, 1601, 1213, 1170 cm^{-1}
NMR ($CDCl_3$, δ) : 7.14 (1H, dd, J=5.1, 3.7Hz), 7.40 (1H, dd, J=5.1, 1.1Hz), 7.47 (1H, dd, J=3.7, 1.1Hz), 7.70-7.82 (2H, m), 7.82-7.96 (2H, m), 10.00 (1H, s)
APCI-MASS : 189 ($M+H^+$)

(9) 4-(Pyrazol-3-yl)benzaldehyde
IR (Neat) : 2400-3700 (br), 1697, 1606, 1211, 1171, 837 cm^{-1}
NMR (DMSO-d_6, δ) : 6.90 (1H, d, J=2.3Hz), 7.83 (1H, br s), 7.85-8.12 (4H, m), 10.00 (1H, s), 13.13 (1H, br)
APCI-MASS (m/z) : 173 ($M+H^+$)

(10) 4-(1-Methylpyrazol-3-yl)benzaldehyde
IR (KBr) : 1695, 1603, 1566, 1431, 1306 cm^{-1}
NMR ($CDCl_3$, δ) : 3.99 (3H, s), 6.64 (1H, d, J=2.3Hz), 7.43 (1H, d, J=2.3Hz), 7.86-8.03 (4H, m), 10.01 (1H, s)
APCI-MASS (m/z) : 187 ($M+H^+$)

(11) 4-(1-Methylpyrazol-5-yl)benzaldehyde
IR (KBr) : 1695, 1608, 1568, 1390, 1215, 1184 cm^{-1}
NMR ($CDCl_3$, δ) : 3.95 (3H, s), 6.41 (1H, d, J=1.9Hz), 7.56 (1H, d, J=1.9Hz), 7.57-7.68 (2H, m), 7.93-8.04 (2H, m), 10.08 (1H, s)
APCI-MASS (m/z) : 187 ($M+H^+$)

(12) 3-(1H-Tetrazol-5-yl)benzaldehyde
IR (KBr) : 2400-3500 (br), 1674, 1612, 1560, 1373, 1207 cm^{-1}
NMR (DMSO-d_6, δ) : 7.86 (1H, dd, J=7.7, 7.7Hz), 8.08-8.20 (1H, m), 8.30-8.42 (1H, m), 8.57 (1H, dd, J=1.5, 1.5Hz), 10.13 (1H, s)
APCI-MASS (m/z) : 175 ($M+H^+$)

Preparation 47

To a suspension of 3-(pyrazol-3-yl)benzonitrile (37.70 g) in formic acid (300 ml) was added a suspension of Raney Nickel (Trademark : NDT-90) in water (130 ml) and the mixture was refluxed for 3.5 hours. The mixture was cooled

to room temperature and Raney Nickel was removed by filtration and washed with formic acid (150 ml). The filtrate was evaporated to dryness and dichloromethane and ice water were added to the residue. The mixture was adjusted to pH ca. 8.5 by addition of 5N sodium hydroxide aqueous solution. The insoluble materials were removed by celite pad and the filtrate was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(pyrazol-3-yl)benzaldehyde (37.17 g).

IR (KBr) : 3190, 2975, 2840, 1690, 1605, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 6.84 (1H, d, J=2.2Hz), 7.65 (1H, dd, J=7.6, 7.6Hz), 7.75-7.85 (2H, m), 7.84 (1H, d, J=7.6Hz), 8.35 (1H, s), 10.07 (1H, s), 13.06 (1H, br s)

Preparation 48

To a solution of 4-fluorobenzaldehyde (2.48 g) and 4-bromophenol (3.46 g) in N,N-dimethylacetamide (20 ml) was added powdered potassium carbonate (2.76 g), and the mixture was refluxed for 17 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(4-bromophenoxy)benzaldehyde (1.51 g).

IR (KBr) : 3030, 2920, 2840, 2735, 1705, 1600, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 6.95-7.1 (4H, m), 7.45-7.55 (2H, m), 7.8-7.9 (2H, m), 9.94 (1H, s)

APCI-MASS (m/z) : 279, 277 ($M+H^+$)

Preparation 49

To a solution of 4-bromobenzaldehyde (4.96 g) and

4-fluorophenol (4.48 g) in N,N-dimethylacetamide (25 ml) was added powdered potassium carbonate (5.53 g), and the mixture was refluxed for 6 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(4-fluorophenoxy)benzaldehyde (1.92 g) as an orange oil.

IR (Film) : 3360, 3075, 2835, 2740, 1695, 1600, 1585, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 6.7-6.8 (1H, m), 6.85-6.95 (1H, m), 7.0-7.2 (4H, m), 7.8-7.9 (2H, m), 9.92 (1H, s)

APCI-MASS (m/z) : 217 ($M+H^+$)

Preparation 50

To a solution of 4-phenylthiobenzonitrile (12.23 g) in toluene (200 ml) was added dropwise diisobutylaluminum hydride (1.02M toluene solution) (114 ml) at -70°C over 50 minutes and the mixture was stirred at -70°C for 30 minutes. To the mixture were added sodium fluoride (19.45 g) and water (6.26 g), and the mixture was warmed to room temperature. The insoluble materials were removed by filtration and washed with toluene. The filtrate was evaporated in vacuo and the residue was dissolved in tetrahydrofuran (50 ml). To this solution was added 6N hydrochloric acid (19.3 ml) and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(phenylthio)benzaldehyde (9.83 g) as a yellow oil.

IR (Film) : 3055, 2830, 2745, 1695, 1595, 1560,

1505 cm^{-1}

NMR ($CDCl_3$, δ) : 7.15-7.3 (4H, m), 7.35-7.6 (3H, m), 7.65-7.75 (2H, m), 9.91 (1H, s)

APCI-MASS (m/z) : 215 ($M+H^+$)

Preparation 51

To a solution of 4-(pyrazol-1-yl)benzonitrile (5.0 g) in dichloromethane (150 ml) was added dropwise diisobutylaluminum hydride (1.02M toluene solution, 58 ml) keeping the temperature below -60°C. After stirring for one hour, sodium fluoride (9.95 g) and water (3.2 ml) were added thereto. The reaction mixture was warmed to room temperature over 30 minutes and stirred for 1.5 hours. Insoluble material was removed by filtration. The filtrate was concentrated by evaporation in vacuo. The residue was dissolved in tetrahydrofuran (25 ml). To he solution was added 1N-hydrochloric acid and stirred for one hour at room temperature. To the mixture was added 5N-sodium hydroxide solution (10 ml). The objective compound was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (100 g, n-hexane - ethyl acetate (1:1)) to give 4-(pyrazol-1-yl)benzaldehyde (4.36 g).

IR (KBr) : 1695, 1605, 1390, 1200 cm^{-1}

NMR ($CDCl_3$, δ) : 6.54 (1H, dd, J=2.5, 1.8Hz), 7.79 (1H, d, J=1.5Hz), 7.85-8.10 (5H, m), 10.02 (1H, s)

APCI-MASS (m/z) : 173 ($M+H^+$)

Preparation 52

The following compound was obtained according to a similar manner to that of Preparation 51.

4-(Imidazol-1-yl)benzaldehyde

IR (KBr) : 1686, 1606, 1522, 1313 cm^{-1}

NMR ($CDCl_3$, δ) : 7.15-8.10 (7H, m), 10.05 (1H, s)

APCI-MASS (m/z) : 173 ($M+H^+$)

Preparation 53

To a solution of methyl 5-phenyl-3-isoxazolecarboxylate (4.73 g) in dichloromethane (150 ml) was added dropwise diisobutylaluminum hydride (1.02M toluene solution 45.7 ml) at -70°C - -60°C. After stirring for one hour at the same temperature, sodium fluoride (7.83 g) and water (2.52 ml) were added thereto. The mixture was warmed to room temperature over 30 minutes and stirred for one hour. Insoluble materials were removed by filtration. The filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (85 g, n-hexane - ethyl acetate (3:1)) to give 5-phenyl-3-isoxazolecarbaldehyde (1.94 g).

IR (KBr) : 3126, 1713, 1568, 1456, 1184 cm^{-1}

NMR ($CDCl_3$, δ) : 6.90 (1H, s), 7.35-7.68 (3H, m), 7.75-7.92 (2H, m), 10.20 (1H, s)

Preparation 54

To the solution of 4-bromobenzaldehyde (462 mg) and 1-methyl-4-tri-n-butylstannylpyrazole (1.1 g) was added tetrakis(triphenylphosphine)palladium(0) (87 mg). Then the mixture was heated for 3 hours at 140°C. After cooling, the reaction mixture was diluted with toluene (6 ml). An aqueous solution (5 ml) of potassium fluoride (1.74 g) was added to the mixture and stirred for one hour. Insoluble material was removed by filtration. The filtrate was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (40 g, eluting with n-hexane - ethyl acetate (1:2)) to give 4-(1-methylpyrazol-4-yl)benzaldehyde (427.4 mg).

IR (KBr) : 1693, 1605, 1169, 831 cm^{-1}

NMR ($CDCl_3$, δ) : 3.98 (3H, s), 7.57-7.67 (2H, m), 7.73 (1H, s), 7.85 (1H, s), 7.80-7.92 (2H, m), 9.98 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

Preparation 55

To a solution of oxalyl chloride (1.5 ml) in dichloromethane (30 ml) was added a solution of dimethyl sulfoxide (1.83 ml) in dichloromethane (4 ml) keeping the temperature below -60°C. After 20 minutes, 4-(oxazol-5-yl)benzyl alcohol (2.5 g) in dichloromethane (25 ml) and dimethyl sulfoxide (2 ml) was added dropwise at the same temperature then stirred for one hour. To the mixture was added triethylamine (8 ml) and stirred for 30 minutes. The reaction mixture was warmed to room temperature over 30 minutes. After stirring for one hour, the mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (80 g, eluting with n-hexane - ethyl acetate (1:1)) to give 4-(oxazol-5-yl)benzaldehyde (2.20 g).

IR (KBr) : 1693, 1610, 1211, 1111, 829 cm^{-1}

NMR ($CDCl_3$, δ) : 7.54 (1H, s), 7.75-8.05 (4H, m), 8.00 (1H, s), 10.03 (1H, s)

APCI-MASS (m/z) : 174 ($M+H^+$)

Preparation 56

To the solution of 3-(1H-tetrazol-5-yl)benzaldehyde (1.0 g) in pyridine (15 ml) was added triphenylchloromethane (1.76 g) at 0-5°C. The mixture was stirred for 4 hours at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with dil. hydrochloric acid, water, brine, dried over magnesium

sulfate, evaporated in vacuo to give 3-(1-trityl-1H-tetrazol-5-yl)benzaldehyde (2.51 g).

IR (KBr) : 1699, 1516, 1491, 1446, 1201 cm^{-1}

NMR (DMSO-d_6, δ) : 7.05-7.20 and 7.38-7.53 (15H, m), 7.80 (1H, dd, J=7.7, 7.7Hz), 8.05-8.14 (1H, m), 8.30-8.40 (1H, m), 8.50-8.55 (1H, m), 10.12 (1H, s)

Preparation 57

The mixture of 4-formylbiphenyl (3.64 g) and cycloheptylamine (2.49 g) was heated at 120°C for 6 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (30 ml). To the solution was added carefully sodium borohydride (757 mg), and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-(4-biphenylylmethyl)cycloheptylamine (5.24 g) as a yellow oil.

IR (Film) : 3030, 2920, 2850 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.5-2.7 (1H, m), 3.72 (2H, s), 7.3-7.7 (9H, m)

APCI-MASS (m/z) : 280 ($M+H^+$)

Preparation 58

The suspension of 4-[4-(dimethylamino)phenyl]-benzaldehyde (640 mg) and cycloheptylamine (643 mg) in toluene (3 ml) was stirred at 120°C for 5 hours under nitrogen. The mixture was evaporated to dryness and dissolved in ethanol (20 ml). To this solution was added sodium borohydride (107 mg) and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was extracted with dichloromethane.

The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cycloheptyl 4-[4-(dimethylamino)phenyl]benzylamine (945 mg).

IR (KBr) : 3275, 3025, 2920, 2850, 2805, 1610, 1535, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.65-2.85 (1H, m), 2.99 (6H, s), 5.79 (2H, s), 6.80 (2H, d, J=8.8Hz), 7.34 (2H, d, J=8.8Hz), 7.45-7.65 (4H, m)

APCI-MASS (m/z) : 323 ($M+H^+$)

Preparation 59

The mixture of 4-phenoxybenzaldehyde (1.98 g) and benzylamine (1.61 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (20 ml). To this solution was added sodium borohydride (378 mg) and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-benzyl-4-phenoxybenzylamine (2.07 g).

IR (Film) : 3035, 2915, 2820, 1680, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 3.78 (2H, s), 3.82 (2H, s), 6.9-7.4 (14H, m)

APCI-MASS (m/z) : 290 ($M+H^+$)

Preparation 60

The mixture of 4-phenoxybenzaldehyde (1.98 g) and furfurylamine (1.61 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (20 ml). To this solution was

added sodium borohydride (378 mg) and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-furfuryl-4-phenoxybenzylamine (2.51 g).

IR (Film) : 3060, 3035, 2920, 2830, 1590, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 3.76 (2H, s), 3.80 (2H, s), 6.15-6.2 (1H, m), 6.3-6.35 (1H, m), 6.9-7.4 (10H, m)

APCI-MASS (m/z) : 280 ($M+H^+$)

Preparation 61

The following compounds were obtained according to similar manners to those of Preparation 57, 58, 59 and 60.

(1) N-(2-Biphenylylmethyl)-cycloheptylamine

IR (Film) : 3060, 3020, 2935, 2910, 2850, 1460 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.8 (12H, m), 2.4-2.6 (1H, m), 3.71 (2H, s), 7.2-7.5 (9H, m)

APCI-MASS (m/z) : 280 ($M+H^+$)

(2) N-Cycloheptyl-4-phenoxybenzylamine

IR (Film) : 3030, 2920, 2850, 1590, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m), 3.75 (2H, s), 6.9-7.4 (9H, m)

APCI-MASS (m/z) : 296 ($M+H^+$)

(3) N-Cyclohexyl-3-phenoxybenzylamine

IR (Film) : 3035, 2925, 2850, 1585 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.75 (2H, s), 6.8-7.4 (9H, m)

APCI-MASS (m/z) : 296 ($M+H^+$)

(4) N-Cycloheptyl-[2-(4-chlorophenyl)thiazol-4-yl]methylamine
IR (KBr) : 2930, 2850, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-2.2 (12H, m), 2.6-2.8 (1H, m), 3.84 (2H, s), 7.49 (1H, s), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)
APCI-MASS (m/z) : 321 ($M+H^+$)

(5) N-Cycloheptyl-(2-phenylimidazol-5-yl)methylamine
IR (KBr) : 3080, 2925, 2855, 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.6-2.75 (1H, m), 3.62 (2H, br s), 6.82 and 7.06 (total 1H, br s), 7.25-7.45 (3H, m), 7.8-7.95 (2H, m), 12.28 (1H, br)
APCI-MASS (m/z) : 270 ($M+H^+$)

(6) N-Cycloheptyl-4-(pyrrol-1-yl)benzylamine
IR (Film) : 2925, 2850, 1610, 1525 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.79 (2H, s), 6.3-6.4 (2H, m), 7.0-7.1 (2H, m), 7.3-7.45 (4H, m)
APCI-MASS (m/z) : 269 ($M+H^+$)

(7) N-Cycloheptyl-3-(pyrrol-1-yl)benzylamine
IR (Film) : 2925, 2850, 1610, 1595, 1545, 1500 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.95 (12H, m), 2.6-2.8 (1H, m), 6.30-6.35 (2H, m), 7.10-7.15 (2H, m), 7.15-7.45 (4H, m)
APCI-MASS (m/z) : 269 ($M+H^+$)

(8) N-Cycloheptyl-[4-(pyrrol-1-yl)pyridin-2-yl]methylamine
IR (Film) : 3305, 3135, 3100, 2925, 2855, 1600, 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-2.0 (12H, m), 2.55-2.7 (1H, m), 3.82 (2H, s), 6.35-6.4 (2H, m), 6.5-6.55 (2H,

m), 6.55-6.6 (1H, m), 6.65-6.7 (1H, d, J=2.2Hz), 8.47 (1H, d, J=5.6Hz)

APCI-MASS (m/z) : 282 ($M+H^+$)

(9) N-Cycloheptyl(6-phenylpyridin-3-yl)methylamine

IR (Film) : 3030, 2910, 2850, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m), 3.83 (2H, s), 7.3-7.5 (2H, m), 7.65-7.8 (2H, m), 7.95-8.05 (2H, m), 8.61 (1H, s)

APCI-MASS (m/z) : 281 ($M+H^+$)

(10) N-Cycloheptyl-3-(pyrazol-3-yl)benzylamine

IR (Film) : 3210, 2915, 2850, 1610, 1540 cm^{-1}

NMR (DMSO-d_6 δ) : 1.3-1.9 (12H, m), 2.5-2.7 (1H, m), 3.72 (2H, s), 6.68 (1H, d, J=2.1Hz), 7.15-7.8 (5H, m)

APCI-MASS (m/z) : 270 ($M+H^+$)

(11) N-Cycloheptyl-4-(4-fluorophenyl)benzylamine

IR (Film) : 2925, 2855, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.65-2.85 (1H, m), 3.81 (2H, s), 7.05-7.2 (2H, m), 7.35-7.6 (6H, m)

APCI-MASS (m/z) : 298 ($M+H^+$)

(12) N-Cycloheptyl-4-(4-chlorophenyl)benzylamine

IR (KBr) : 3030, 2925, 2855, 1485 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.0 (12H, m), 2.6-2.8 (1H, m), 3.82 (2H, s), 7.4-7.6 (8H, m)

APCI-MASS (m/z) : 314 ($M+H^+$)

(13) N-Cycloheptyl-4-(4-bromophenyl)benzylamine

IR (KBr) : 3035, 2925, 2855, 1480 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.81 (2H, s), 7.35-7.65 (8H, m)

APCI-MASS (m/z) : 360, 358 ($M+H^+$)

(14) N-Cycloheptyl-4-(4-methylphenyl)benzylamine
IR (Film) : 3025, 2910, 2855, 1500 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.39 (3H, s), 2.65-2.8 (1H, m), 3.81 (2H, s), 7.24 (2H, d, J=7.6Hz), 7.37 (2H, d, J=8.3Hz), 7.4-7.6 (4H, m)
APCI-MASS (m/z) : 294 ($M+H^+$)

(15) N-Cycloheptyl-4-(4-bromophenoxy)benzylamine
IR (Film) : 3030, 2925, 2850, 1585, 1505, 1480 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.75 (2H, s), 6.8-7.0 (4H, m), 7.25-7.5 (4H, m)
APCI-MASS (m/z) : 376, 374 ($M+H^+$)

(16) N-Cycloheptyl-4-(4-phenylthio)benzylamine
IR (Film) : 2920, 2850, 1510 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.55-2.75 (1H, m), 3.75 (2H, s), 7.2-7.5 (9H, m)
APCI-MASS (m/z) : 312 ($M+H^+$)

(17) N-Cycloheptyl-(6-phenylthiopyridin-3-yl)methylamine
IR (Film) : 3305, 2925, 2850, 1700, 1585, 1560 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.55-2.75 (1H, m), 3.71 (2H, s), 6.87 (1H, d, J=8.2Hz), 7.4-7.7 (6H, m), 8.35-8.4 (1H, m)
APCI-MASS (m/z) : 313 ($M+H^+$)

(18) N-Cycloheptyl-4-(4-benzoylamino)benzylamine
IR (Film) : 3265, 3150, 3070, 2925, 2850, 1645, 1615, 1595, 1555 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.55-2.7 (1H, m), 3.69 (2H, s), 7.07 (1H, d, J=7.7Hz), 7.27 (1H, t, J=7.7Hz), 7.5-7.8 (5H, m), 7.9-8.0 (2H, m), 10.22 (1H, s)

APCI-MASS (m/z) : 323 ($M+H^+$)

(19) N-Cycloheptyl-4-(2-pyridylcarbamoyl)benzylamine
IR (KBr) : 3305, 2925, 2855, 1680, 1610, 1580, 1535, 1505 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.5-2.7 (1H, m), 3.76 (2H, s), 7.17 (1H, dd, J=6.3, 4.9Hz), 7.45 (2H, d, J=8.2Hz), 7.98 (2H, d, J=8.2Hz), 7.8-7.9 (1H, m), 8.19 (1H, d, J=8.4Hz), 8.35-8.4 (1H, m), 10.70 (1H, s)
APCI-MASS (m/z) : 324 ($M+H^+$)

(20) N-Cycloheptyl-4-(4-fluorophenoxy)benzylamine
IR (Film) : 2925, 2855, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.65-2.8 (1H, m), 3.75 (2H, s), 6.85-7.1 (6H, m), 7.2-7.35 (2H, m)
APCI-MASS (m/z) : 314 ($M+H^+$)

(21) N-Cycloheptyl-4-(phenylsulfamoyl)benzylamine
NMR (DMSO-d_6, δ) : 1.2-1.8 (12H, m), 2.5-2.6 (1H, m), 3.70 (2H, s), 7.0-7.15 (3H, m), 7.15-7.25 (2H, m), 7.47 (2H, d, J=8.3Hz), 7.68 (2H, d, J=8.3Hz), 10.23 (1H, s)
APCI-MASS (m/z) : 359 ($M+H^+$)

(22) N-Cycloheptyl-4-(3-thienyl)benzylamine
IR (KBr) : 2924, 1458, 1201, 775 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.62-2.78 (1H, m), 3.80 (2H, s), 7.30-7.47 (5H, m), 7.50-7.60 (2H, m)
APCI-MASS (m/z) : 286 ($M+H^+$)

(23) N-Cycloheptyl-4-(2-thienyl)benzylamine
IR (Neat) : 2924, 1502, 1458, 1101, 810 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.62-2.78 (1H,

m), 3.79 (2H, s), 7.07 (1H, dd, J=5.1, 3.6Hz), 7.22-7.40 (4H, m), 7.50-7.65 (2H, m)
APCI-MASS (m/z) : 286 ($M+H^+$)

(24) N-Cycloheptyl-4-(pyrazol-1-yl)benzylamine
IR (Neat) : 2927, 1610, 1525, 1460, 1394 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.95 (12H, m), 2.60-2.78 (1H, m), 3.81 (2H, s), 6.46 (1H, t, J=2.1Hz), 7.36-7.46 (2H, m), 7.58-7.68 (2H, m), 7.71 (1H, d, J=1.6Hz), 7.91 (1H, d, J=2.1Hz)
APCI-MASS (m/z) : 270 ($M+H^+$)

(25) N-Cycloheptyl-4-(imidazol-1-yl)benzylamine
IR (Neat) : 2922, 1522, 1303, 1057 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.60-2.80 (1H, m), 3.83 (2H, s), 7.20 (1H, d, J=1.0Hz), 7.27 (1H, d, J=1.0Hz), 7.30-7.50 (4H, m), 7.84 (1H, s)
APCI-MASS (m/z) : 270 ($M+H^+$)

(26) N-Cycloheptyl-4-(1-methylpyrazol-4-yl)benzylamine
IR (KBr) : 3277, 2924, 1572, 1443, 1194, 802 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-2.20 (12H, m), 2.62-2.80 (1H, m), 3.78 (2H, s), 3.94 (3H, s), 7.27-7.47 (4H, m), 7.58 (1H, s), 7.74 (1H, s)
APCI-MASS (m/z) : 284 ($M+H^+$)

(27) N-Cycloheptyl-2-(2-phenylthiophen-5-yl)methylamine
IR (Neat) : 2924, 1599, 1462, 754 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.66-2.85 (1H, m), 3.98 (2H, s), 6.87 (1H, d, J=3.6Hz), 7.15 (1H, d, J=3.6Hz), 7.18-7.45 (3H, m), 7.52-7.64 (2H, m)
APCI-MASS (m/z) : 286 ($M+H^+$)

(28) N-Cycloheptyl-4-(oxazol-5-yl)benzylamine

IR (KBr) : 2924, 1510, 1485, 1103, 822 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.60-2.80 (1H, m), 3.81 (2H, s), 7.33 (1H, s), 7.33-7.46 (2H, m), 7.55-7.69 (2H, m), 7.90 (1H, s)

APCI-MASS (m/z) : 271 ($M+H^+$)

(29) N-Cycloheptyl-(2-phenylfuran-5-yl)methylamine

IR (Neat) : 2924, 1545, 1456, 1020, 760 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.95 (12H, m), 2.64-2.80 (1H, m), 3.84 (2H, s), 6.24 (1H, d, J=3.3Hz), 6.57 (1H, d, J=3.3Hz), 7.17-7.45 (3H, m), 7.58-7.72 (2H, m)

APCI-MASS (m/z) : 270 ($M+H^+$)

(30) N-Cycloheptyl-(5-phenylisoxazol-3-yl)methylamine

IR (Neat) : 2926, 2854, 1616, 1574, 1456, 1113, 766 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.65-2.82 (1H, m), 3.90 (2H, s), 6.53 (1H, s), 7.34-7.53 (3H, m), 7.70-7.86 (2H, m)

APCI-MASS (m/z) : 271 ($M+H^+$)

(31) N-Cycloheptyl-(3-phenylpyrazol-5-yl)methylamine

IR (Neat) : 2300-3600 (br), 1570, 1460, 1358, 1026 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.65-2.82 (1H, m), 3.92 (2H, s), 6.46 (1H, s), 7.20-7.50 (3H, m), 7.64-7.80 (2H, m)

APCI-MASS (m/z) : 270 ($M+H^+$)

(32) N-Cycloheptyl-(4-phenylthiophen-2-yl)methylamine

IR (Neat) : 2924, 2852, 1502, 1458, 1367, 841, 735 cm^{-1}

NMR ($CDCl_3$, δ) : 1.32-1.98 (12H, m), 2.70-2.88 (1H, m), 4.01 (2H, s), 7.19-7.62 (7H, m)

APCI-MASS (m/z) : 286 ($M+H^+$)

(33) N-Cycloheptyl-4-(pyrazol-3-yl)benzylamine

IR (Neat) : 2300-3600 (br), 1514, 1456, 1350, 1205 cm^{-1}

NMR (DMSO-d_6, δ) : 1.20-1.93 (12H, m), 2.50-2.72 (1H, m), 3.73 (2H, s), 6.67 (1H, d, J=1.9Hz), 7.30-7.90 (5H, m), 12.70-13.40 (1H, br)

APCI-MASS (m/z) : 270 ($M+H^+$)

(34) N-Cycloheptyl-4-(1-methylpyrazol-3-yl)benzylamine

IR (KBr) : 2922, 2852, 1510, 1462, 1429, 1358, 1234 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.61-2.78 (1H, m), 3.80 (2H, s), 3.95 (3H, s), 6.52 (1H, d, J=2.2Hz), 7.29-7.40 (3H, m), 7.70-7.80 (2H, m)

APCI-MASS (m/z) : 284 ($M+H^+$)

(35) N-Cycloheptyl-4-(1-methylpyrazol-5-yl)benzylamine

IR (Neat) : 2924, 2854, 1493, 1462, 1385, 1273 cm^{-1}

NMR ($CDCl_3$, δ) : 1.32-1.98 (12H, m), 2.62-2.81 (1H, m), 3.83 (2H, s), 3.89 (3H, s), 6.29 (1H, d, J=1.9Hz), 7.33-7.46 (4H, m), 7.51 (1H, d, J=1.9Hz)

APCI-MASS (m/z) : 284 ($M+H^+$)

(36) N-Cycloheptyl-3-(1-trityl-1H-tetrazol-5-yl)benzylamine

IR (KBr) : 2922, 2852, 1697, 1515, 1452, 750, 698 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.95 (12H, m), 2.62-2.78 (1H, m), 3.83 (2H, s), 7.10-7.50 (17H, m), 7.96-8.12 (2H, m)

FAB-MASS (m/z) : 514 ($M+H^+$)

(37) N-Cycloheptyl-4-(phenylcarbamoyl)benzylamine

IR (KBr) : 3475, 3345, 3055, 2925, 2850, 1645, 1600, 1525, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.5-2.65 (1H, m), 3.78 (2H, s), 7.09 (1H, t, J=7.3Hz), 7.35 (2H, s), 7.48 (2H, d, J=8.2Hz), 7.78 (2H, d, J=7.5Hz), 7.90 (2H, d, J=8.2Hz), 10.20 (1H, s)

APCI-MASS (m/z) : 323 ($M+H^+$)

(38) N-Cycloheptyl-4-(phenylsulfonylamino)benzylamine

IR (KBr) : 3130, 3015, 2930, 2855, 1610, 1570, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 1.2-1.8 (12H, m), 2.5-2.6 (1H, m), 3.58 (2H, s), 6.99 (2H, d, J=8.5Hz), 7.16 (2H, d, J=8.5Hz), 7.45-7.6 (3H, m), 7.65-7.75 (2H, m)

APCI-MASS (m/z) : 359 ($M+H^+$)

Preparation 62

The mixture of 4-formyl-2-(4-chlorophenyl)thiazole (2.24 g) and benzylamine (2.14 g) was stirred at 120°C under nitrogen for 5 hours. The mixture was cooled to room temperature and dissolved in ethanol (30 ml). To this solution was added sodium borohydride (378 mg) and the mixture was stirred at room temperature for 1.1 hours. The mixture was evaporated to dryness and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography to give N-benzyl-[2-(4-chlorophenyl)thiazol-4-yl]methylamine (3.22 g).

IR (Film) : 3060, 3030, 2915, 2835, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.64 (1H, br s), 3.67 (2H, s), 3.78 (2H, s), 7.2-7.4 (5H, m), 7.52 (1H, s), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

APCI-MASS (m/z) : 315 ($M+H^+$)

Preparation 63

The mixture of 3-bromomethylbiphenyl (6.58 g) and cycloheptylamine (6.03 g) was stirred at 120°C for 3.5 hours under nitrogen. The mixture was cooled to room temperature, and the mixture of dichloromethane and water were added thereto. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-(3-biphenylylmethyl)-cycloheptylamine (4.49 g) as an orange oil.

IR (Film) : 3060, 3030, 2920, 2850, 1460 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.7-2.85 (1H, m), 3.85 (2H, s), 7.3-7.7 (9H, m)

APCI-MASS (m/z) : 280 ($M+H^+$)

Preparation 64

The following compounds were obtained according to similar manners to those of Preparations 62 and 63.

(1) N-Cycloheptyl-4-(pyridin-3-yl)benzylamine

NMR ($CDCl_3$, δ) : 1.3-1.9 (12H, m), 2.9-3.05 (1H, m), 7.3-7.6 (5H, m), 7.8-7.9 (1H, m), 8.5-8.6 (1H, m), 8.8-8.85 (1H, m)

APCI-MASS (m/z) : 281 ($M+H^+$)

(2) N-Cycloheptyl-4-(pyridin-2-yl)benzylamine

IR (Film) : 3050, 3005, 2920, 2850, 1585, 1565 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.3-1.9 (12H, m), 2.6-2.7 (1H, m), 3.74 (2H, s), 7.25-7.5 (3H, m), 7.8-8.1 (4H, m), 8.6-8.7 (1H, m)

APCI-MASS (m/z) : 281 ($M+H^+$)

(3) N-Cycloheptyl-4-(4-benzoyl)benzylamine

IR (Film) : 3050, 2925, 2850, 1655, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m),

3.87 (2H, s), 7.4-7.65 (5H, m), 7.75-7.9 (4H, m)
APCI-MASS (m/z) : 308 ($M+H^+$)

Preparation 65

To a solution of 3-(2-methylthiazol-4-yl)-benzylamine·hydrochloride (2.41 g) in a mixture of dichloromethane (30 ml) and water (10 ml) was added 5N sodium hydroxide aqueous solution and adjusted to pH 9-10. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. To the residual oil was added cycloheptanone (1.68 g) and the mixture was stirred at 120°C under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (30 ml). To this solution was added sodium borohydride (378 mg) and the mixture was stirred at room temperature for 2.5 hours. The mixture was evaporated to dryness and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatogaphy on silica gel to give N-cycloheptyl-3-(2-methylthiazol-4-yl)benzylamine (2.07 g) as a yellow oil.

IR (Film) : 3380, 2915, 2855, 1455 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-2.0 (12H, m), 2.7-2.85 (1H, m), 2.76 (3H, s), 3.82 (2H, s), 7.32 (1H, s), 7.25-7.4 (2H, m), 7.75-7.9 (2H, m)
APCI-MASS (m/z) : 301 ($M+H^+$)

Preparation 66

To a suspension of N-cycloheptyl-4-(4-benzoyl)benzylamine (1.87 g) in ethylene glycol (10 ml) were added potassium hydroxide (511 mg) and hydrazine monohydrate (1.95 g), and the mixture was stirred at 150°C for 5 hours and at 200°C for 4 hours. The mixture was poured into a mixture of dichloromethane and ice water, and the separated organic layer was washed with water and

brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cycloheptyl-4-(4-benzyl)benzylamine (1.29 g) as an orange oil.

IR (Film) : 3025, 2905, 2850, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m), 3.74 (2H, s), 3.96 (2H, s), 7.1-7.4 (9H, m)

APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 67

To a solution of 3-(pyrazol-3-yl)benzaldehyde (4.33 g) in pyridine (20 ml) was added trityl chloride (7.71 g) under ice cooling. The mixture was stirred for 30 minutes, and then warmed to room temperature. After stirring for 3 hours at the same temperature, the reaction mixture was poured into ice aqueous hydrochloric acid, extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with n-hexane - ethyl acetate (2:1)) to give 3-(1-tritylpyrazol-3-yl)benzaldehyde (9.26 g).

IR (KBr) : 3477, 3060, 3030, 1697, 1601, 1491, 1444 cm^{-1}

NMR (DMSO-d_6, δ) : 6.93 (1H, d, J=2.5Hz), 7.1-7.5 (16H, m), 7.63 (1H, dd, J=7.7, 7.7Hz), 7.85 (1H, d, J=7.7Hz), 8.08 (1H, d, J=7.7Hz), 8.25 (1H, s), 10.04 (1H, s)

Preparation 68

The mixture of 3-(1-tritylpyrazol-3-yl)benzaldehyde (15.31 g) and benzylamine (7.91 g) was stirred at 120°C for 5 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (120 ml). To this solution was added carefully sodium borohydride (1.40 g) at room temperature and the mixture was stirred for 2 hours.

The mixture was concentrated in vacuo and to the residue were added dichloromethane and ice water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-benzyl-3-(1-tritylpyrazol-3-yl)benzylamine (12.18 g) as an amorphous solid.

IR (KBr) : 3059, 3028, 1599, 1493 cm^{-1}

NMR (DMSO-d_6, δ) : 3.65-3.75 (4H, m), 6.77 (1H, d, J=2.5Hz), 7.05-7.45 (18H, m), 7.55-7.75 (2H, m)

Preparation 69

To a suspension of N-benzyl-3-(1-tritylpyrazol-3-yl)benzylamine (8.60 g) in anisole (17.2 ml) was added trifluoroacetic acid (34.4 ml) at room temperature and the mixture was stirred at 80°C for 3.5 hours. The mixture was concentrated in vacuo and the residue was pulverized with diisopropyl ether. The powder was collected by filtration, washed with diisopropyl ether and dried in vacuo to give N-benzyl-3-(pyrazol-3-yl)benzylamine bis(trifluoroacetate) (7.35 g).

IR (KBr) : 3059, 3005, 1669, 1510, 1489 cm^{-1}

NMR (DMSO-d_6, δ) : 4.2-4.3 (4H, m), 6.70-6.75 (1H, m), 7.1-7.6 (7H, m), 7.75-8.0 (3H, m)

Preparation 70

To a solution of 2,4-dichloro-6-methyl-3-nitropyridine (30.33 g) in acetonitrile (100 ml) was added dropwise sodium methoxide (28% methanol solution) (85.1 ml) at 5°C, and the mixture was stirred at 80°C for 6 hours. The mixture was cooled and poured into a mixture of ethyl acetate and ice water. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 2,4-dimethoxy-

6-methyl-3-nitropyridine (28.21 g) as a pale yellow crystal.

IR (KBr) : 3093, 3035, 3005, 2960, 2868, 1601, 1581, 1531 cm^{-1}

NMR (DMSO-d_6, δ) : 2.44 (3H, s), 3.92 and 3.94 (6H, s x 2), 6.97 (1H, s)

APCI-MASS (m/z) : 199 ($M+H^+$)

Preparation 71

To a solution of 2,4-dimethoxy-6-methyl-3-nitropyridine (28.1 g) in 1,4-dioxane (200 ml) and methanol (100 ml) was added 10% palladium on carbon (14 g) under nitrogen and the mixture was hydrogenated under atmospheric pressure for 4.5 hours. Palladium on carbon was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-amino-2,4-dimethoxy-6-methylpyridine (23.41 g) as an orange oil.

IR (Film) : 3458, 3373, 2945, 2856, 1605 cm^{-1}

NMR (DMSO-d_6, δ) : 2.26 (3H, s), 3.79 and 3.82 (6H, s x 2), 3.96 (2H, br s), 6.52 (1H, s)

APCI-MASS (m/z) : 169 ($M+H^+$)

Preparation 72

To a solution of 3-amino-2,4-bis(methylthio)-6-methylpyridine (7.90 g) in dichloromethane (160 ml) was added N,N-dimethylaniline (5.73 g) at 5°C, followed by dropwise addition of phenyl chloroformate (6.78 g). The mixture was warmed to room temperature and stirred at 4 hours. To the mixture were added ice water (60 ml) and 6N hydrochloric acid (10 ml), and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized, and the crystal was collected by filtration, washed with diisopropyl ether and dried in vacuo to give 3-

phenoxycarbonylamino-2,4-bis(methylthio)-6-methylpyridine (10.46 g).

IR (KBr) : 3410, 3228, 3196, 3145, 3003, 2926, 1732, 1591, 1556, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 2.45 (6H, s), 2.46 (3H, s), 6.94 (1H, s), 7.0-7.5 (5H, m), 9.48 (1H, br s)

APCI-MASS (m/z) : 321 ($M+H^+$)

Preparation 73

To a solution of 2,4,6-trifluoroaniline (883 mg) and N,N-dimethylaniline (0.91 ml) in methylene chloride (18 ml) was added phenyl chloroformate (0.83 ml) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was washed with 1N-hydrochloric acid (three times), water, aqueous sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The resulting solid was collected and washed with n-hexane to give phenyl N-(2,4,6-trifluorophenyl)carbamate (1.46 g).

IR (KBr) : 3253, 1749, 1722, 1538, 1240, 1200 cm^{-1}

NMR ($CDCl_3$, δ) : 6.26 (1H, br s), 6.70-6.86 (2H, m), 7.10-7.46 (5H, m)

APCI-MASS (m/z) : 268 ($M+H^+$)

Preparation 74

To a solution of 3-amino-2,4-dimethoxy-6-methylpyridine (23.40 g) in dichloromethane (200 ml) was added N,N-dimethylaniline (20.23 g), followed by dropwise addition of phenyl chloroformate (23.94 g) at 5°C. The mixture was warmed to room temperature and stirred for 3 hours. The resulting precipitates were collected by filtration, washed with dichloromethane and diisopropyl ether, and dried in vacuo to give 2,4-dimethoxy-6-methyl-3-phenoxycarbonylaminopyridine (21.95 g) as a white crystal.

IR (KBr) : 3408, 3251, 3147, 3064, 2983, 2947, 2860,

1713, 1593, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 3.85 (6H, s), 6.72 (1H, s), 7.05-7.3 (3H, m), 7.35-7.45 (2H, m), 8.83 (1H, br)

APCI-MASS (m/z) : 289 ($M+H^+$)

Preparation 75

A mixture of 4-(4-bromophenoxy)benzaldehyde (10.0 g) and benzylamine (5.42 g) was stirred at 120°C for 4 hours. After cooling to room temperature, the resulting solid was suspended in ethanol (150 ml). To the suspension was added carefully sodium borohydride (1.36 g), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with methylene chloride. The organic layer was washed with water, brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (250 g, eluting with methylene chloride - methanol (20:1)) to give N-benzyl-4-(4-bromophenoxy)benzylamine (11.51 g) as a pale yellow oil.

IR (Neat) : 3061, 3028, 2700-3000 (br), 1608, 1583, 1504, 1481, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 3.79 (2H, s), 3.82 (2H, s), 6.80-7.00 (4H, m), 7.20-7.50 (9H, m)

APCI-MASS (m/z) : 368, 370 ($M+H^+$)

Preparation 76

The mixture of 3-(1-tritylpyrazol-3-yl)benzaldehyde (9.18 g) and cycloheptylamine (3.75 g) was stirred at 120°C for 4 hours. The mixture was cooled to room temperature and dissolved in ethanol (120 ml). To this solution was added sodium borohydride (836 mg) and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and extracted with methylene chloride. The organic layer was washed with water and brine, dried

over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with methylene chloride - methanol (40:1 to 10:1)) to give N-cycloheptyl-3-(1-tritylpyrazol-3-yl)benzylamine (7.92 g).

NMR (DMSO-d_6, δ) : 1.20-1.90 (12H, m), 2.50-2.70 (1H, m), 3.69 (2H, s), 6.77 (1H, d, J=2.5Hz), 7.05-7.50 (12H, m), 7.55-7.65 (1H, m), 7.71 (1H, s)

APCI-MASS (m/z) : 512 ($M+H^+$)

Preparation 77

To a suspension of 3-amino-2,4,6-trimethylpyridine·hydrochloride (5.18 g) in 1,2-dichloroethane (120 ml) was added diisopropylethylamine (19.39 g) at room temperature, followed by addition of phenyl chloroformate (7.05 g). The mixture was refluxed for 10 hours under nitrogen. The mixture was cooled and poured into ice water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-phenoxycarbonylamino-2,4,6-trimethyl pyridine as a crude orange oil (3.17 g).

IR (KBr) : 3275, 2924, 1740, 1713, 1605, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.39 (6H, s), 7.01 (1H, s), 7.2-7.6 (5H, m), 9.42 (1H, brs)

APCI-MASS (m/z) : 257 ($M+H^+$)

Preparation 78

To a suspension of 4-chloro-6-methyl-2-methylthio-3-nitropyridine (16.0 g) in a mixture of 1,4-dioxane (200 ml) and methanol (50 ml) was added Raney-Nickel (NDT-90; trademark: Kawaken fine chemicals) (ca. 30 g) under nitrogen, and the mixture was hydrogenated under atomospheric pressure for 3 hours. Raney-Nickel was

filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-amino-2-chloro-6-methyl-4-methylthiopyridine (12.86 g) as an orange oil.

IR (film) : 3424, 3322, 2922, 1707, 1606, 1570, 1529 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.31 (3H, s), 4.93 (2H, brs), 6.98 (1H, s)

APCI-MASS (m/z) : 191, 189 ($M+H^+$)

Preparation 79

To a solution of 3-amino-4-chloro-6-methyl-2-methylthiopyridine (12.75 g) in dichloromethane (200 ml) was added N,N-dimethylaniline (6.00 g) at 5°C, followed by dropwise addition of phenylchloroformate (7.11 g). The mixture was warmed to room temperature and stirred at the same temperature for 4 hours. The mixture was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether and collected by filtration, washed with diisopropyl ether and dried in vacuo under phosphorus pentoxide to give 2-chloro-6-methyl-4-methylthio-3-phenoxycarbonylaminopyridine (9.58 g).

IR (KBr) : 3194, 2924, 1751, 1579, 1514, 1489 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.50 (3H, s), 6.7-6.85 (3H, m), 6.98 (1H, s), 7.1-7.25 (2H, m), 9.35 (1H, brs)

Preparation 80

To a solution of 3,5-di-tert-butyl-4-hydroxyphenol (9.65 g) and imidazole (3.55 g) in N,N-dimethylformamide (80 ml) was added tert-butyldimethylsilyl chloride (6.54 g) at 5°C, and the mixture was stirred at room temperature for 3 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was

washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-tert-butyldimethylsilyloxy-3,5-di-tert-butyl-4-hydroxybenzene (13.91 g) as a white solid.

IR (KBr) : 3651, 2958, 2929, 2858, 1601, 1470 cm^{-1}

NMR ($CDCl_3$, δ) : 0.18 (6H, s), 0.91 (9H, s), 1.41 (18H, s), 6.73 (2H, s)

APCI-MASS (m/z) : 336 (M^+)

Preparation 81

To a suspension of sodium hydride (60% oil dispersion) (1.65 g) in N,N-dimethylformamide (100 ml) was added dropwise a solution of 1-tert-butyldimethylsilyloxy-3,5-di-tert-butyl-4-hydroxybenzene (13.89 g) in N,N-dimethylformamide (70 ml) at 5°C, and the mixture was stirred at the same temperature for 1 hour. To the resulting solution was added chloromethyl methyl ether (4.99 g) at 5°C and the mixture was stirred at room temperature for 5 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-tert-butyldimethylsilyloxy-3,5-di-tert-butyl-4-methoxy methoxybenzene (13.49 g) as a yellow solid.

IR (KBr) : 2962, 2929, 2897, 2860, 1597 cm^{-1}

NMR ($CDCl_3$, δ) : 0.19 (6H, s), 0.98 (9H, s), 1.41 (18H, s), 3.62 (3H, s), 4.86 (2H, s), 6.72 (2H, s)

APCI-MASS (m/z) : 381 ($M+H^+$)

Preparation 82

To a solution of 1-tert-butyldimethylsilyloxy-3,5-di-tert-butyl-4-methoxymethoxybenzene (13.42 g) in

tetrahydrofuran (20 ml) was added 1.0M solution of tetrabutylammonium fluoride (38.8 ml) at room temperature and the mixture was stirred at the same temperature for 2 hours. The mixture was poured into a mixture of ethyl acetate and ice water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3,5-di-tert-butyl-4-methoxymethoxyphenol (9.43 g) as a yellow crystal.

IR (KBr) : 3369, 3012, 2958, 2910, 2870, 2779, 1610, 1589 cm^{-1}

NMR ($CDCl_3$, δ) : 1.42 (18H, s), 3.63 (3H, s), 4.87 (2H, s), 6.74 (2H, s)

Preparation 83

To a solution of 1-(4-fluorophenoxy)-4-nitrobenzene (22.9 g) in ethyl acetate (200 ml) was added 10% palladium-carbon (50% wet) (9.16 g), and the mixture was hydrogenated under atmospheric pressure at room temperature for 3 hours. Palladium on carbon was filtered off and washed with tetrahydrofuran. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 4-(4-fluorophenoxy)aniline (18.27 g) as a red powder.

IR (KBr) : 3450, 3395, 3325, 3230, 3070 3045, 3020, 1635, 1490 cm^{-1}

NMR ($CDCl_3$, δ) : 6.65-6.75 (2H, m), 6.8-7.05 (6H, m)

APCI-MASS (m/z) : 204 ($M+H^+$)

Preparation 84

To a solution of 3-(4-fluorophenoxy)benzyl alcohol (3.97 g) in chloroform (50 ml) was added activated manganese dioxide (15.82 g) and the mixture was refluxed for 4.5 hours. Manganese dioxide was filtered off and the filtrate was evaporated in vacuo to give crude 3-(4-

fluorophenoxy)benzaldehyde (3.81 g) as a yellow oil.

IR (Film) : 3074, 2837, 2819, 2731, 1701, 1585, 1502, 1481, 1450 cm^{-1}

NMR (DMSO-d_6, δ) : 7.1-7.45 (6H, m), 7.55-7.75 (2H, m), 9.98 (1H, s)

Preparation 85

To a suspension of lithium aluminum hydride (5.69 g) in tetrahydrofuran (300 ml) was added dropwise a solution of 4-(4-fluorophenoxy)benzonitrile (21.32 g) in tetrahydrofuran (200 ml) at 5°C, and the mixture was stirred at room temperature for 4 hours. To the mixture was added sodium fluoride (16.80 g), followed by dropwise addition of cold water (5.41 g) and the mixture was stirred at room temperature for 45 minutes. The insoluble materials were filtered off and washed with tetrahydrofuran. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 4-(4-fluorophenoxy)benzylamine (21.39 g) as a yellow oil.

IR (KBr) : 3352, 3269, 3043, 2864, 1645, 1606, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 3.69 (2H, s), 6.9-7.4 (8H, m)

APCI-MASS (m/z) :201 ($M+H^+-NH_3$)

Preparation 86

To a solution of phenyl chloroformate (31.2 g) in 1,2-dichloroethane (250 ml) was added dropwise a solution of 3-amino-2,4,6-trimethylpyridine (22.62 g) in 1,2-dichloroethane (120 ml) at 100°C, and the mixture was refluxed for 1 hour under nitrogen. The mixture was cooled to room temperature and added dropwise a mixture of ethyl acetate (2 ℓ) and tetrahydrofuran (1 ℓ). The precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether and dried in vacuo over phosphorus

pentoxide to give 2,4,6-trimethyl-3-phenoxycarbonylaminopyridine·hydrochloride (48.84 g).

IR (KBr) : 3413, 1741, 1645, 1541, 1483 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 2.69 (6H, s), 7.2-7.5 (5H, m), 7.65-7.75 (1H, m), 9.63 and 10.20 (total 1H, br s)

APCI-MASS (m/z) : 257 ($M+H^+$-HCl)

Preparation 87

To a solution of 5-amino-4,6-bis(methylthio)-2-methylpyrimidine (4.10 g) in dichloromethane (80 ml) was added N,N-dimethylaniline (2.96 g) at 5°C, followed by dropwise addition of phenyl chloroformate (3.51 g). The mixture was stirred at room temperature for 2 hours under nitrogen. The mixture was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether collected by filtration, washed with diisopropyl ether and dried in vacuo to give 4,6-bis(methylthio)-2-methyl-5-phenoxycarbonylaminopyrimidine (5.74 g).

IR (KBr) : 3217, 3005, 2924, 1711, 1595, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (6H, s), 2.59 (3H, s), 7.0-7.5 (5H, m), 9.27 and 9.68 (total 1H, s)

APCI-MASS (m/z) : 322 ($M+H^+$)

Preparation 88

To a solution of 2-(3-bromophenyl)-1,3-dioxolane (20.42 g) and triisopropoxyborane (25.14 g) in tetrahydrofuran (350 ml) was added dropwise n-butyllithium (1.70M hexane solution, 78.8 ml) at -72°C over 2-hours under nitrogen. The mixture was warmed to room temperature and stirred for 21 hours. The mixture was poured into a mixture of ethyl acetate and dilute hydrochloric acid and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in

vacuo. The residue was purified by column chromatography on silica gel to give crude dihydroxy-(3-formylphenyl)-borane (14.83 g).

IR (KBr) : 3354, 2840, 1678, 1603, 1581 cm^{-1}

NMR (DMSO-d_6, δ) : 7.55-7.7 (1H, m), 7.8-8.15 (2H, m), 8.33 (2H, s), 10.03 (1H, s)

Preparation 89

To a suspension of 4-bromo-1-tritylpyrazole (18.96 g) and crude dihydroxy-(3-formylphenyl)borane (14.6 g) in toluene (400 ml) were added powdered potassium carbonate (10.10 g) and tetrakis(triphenylphosphine)palladium(0) (2.81 g), and the mixture was refluxed for 6 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(1-tritylpyrazol-4-yl)benzaldehyde (2.65 g) as a yellow solid.

IR (KBr) : 3057, 3024, 2812, 2727, 1699, 1603, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 7.0-7.15 (5H, m), 7.35-7.5 (10H, m), 7.7-7.85 (2H, m), 7.97 (1H, d, J=7.7Hz), 8.13 (1H, d, J=7.7Hz), 8.31 (1H, s), 10.13 (1H, s)

Preparation 90

To a solution of 3-bromobenzaldehyde (1.25 g) and 1-methyl-4-tri-n-butylstanniopyrazole (3.0 g) was added tetrakis(triphenylphosphine)palladium(0) (234 mg). Then the mixture was heated for 4 hours at 140°C. After cooling, the reaction mixture was diluted with toluene (16 ml). An aqueous solution (14 ml) of potassium fluoride (4.7 g) was added to the mixture and stirred for one hour. Insoluble material was filtered off. The filtrate was washed with water and brine, dried over magnesium sulfate,

and evaporated in vacuo. The residue was chromatographed on silica gel (60 g, eluting with n-hexane - ethyl acetate (1:2)) to give 3-(1-methylpyrazol-4-yl)benzaldehyde (978.1 mg).

IR (Neat) : 2943, 2818, 1686, 1608, 1230, 1174 cm^{-1}

NMR ($CDCl_3$, δ) : 3.98 (3H, s), 7.47-7.58 (1H, m), 7.65-7.78 (3H, m), 7.83 (1H, s), 7.93-7.98 (1H, m), 10.04 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

Preparation 91

To a solution of 3-[(E)-3-dimethylaminopropenoyl]-benzonitrile (8 g) in acetic acid (80 ml) was added methylhydrazine (2.23 ml). The mixture was stirred for 3.5 hours at room temperature. To the solution was added 5N-sodium hydroxide aqueous solution in order to basify under ice cooling and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, water, brine, dried over magnesium sulfate, evaporated in vacuo. After chromatography on silica gel (eluting with dichloromethane-methanol), 3-(1-methylpyrazol-3-yl)benzonitrile (4.45 g) and 3-(1-methylpyrazol-5-yl)benzonitrile (2.09 g) were obtained.

3-(1-Methylpyrazol-3-yl)benzonitrile;

mp : 97-98°C

IR (KBr) : 3115, 2935, 2220, 1602, 1471, 1352, 1246 cm^{-1}

NMR ($CDCl_3$, δ) : 3.97 (3H, s), 6.56 (1H, d, J=2.3Hz), 7.37-7.60 (3H, m), 7.95-8.10 (2H, m)

APCI-MASS (m/z) : 184 ($M+H^+$)

3-(1-Methylpyrazol-5-yl)benzonitrile;

mp : 95-97°C

IR (KBr) : 3066, 2951, 2231, 1475, 1416, 1335,

1236 cm^{1}

NMR ($CDCl_3$, δ) : 3.92 (3H, s), 6.37 (1H, d, J=1.5Hz), 7.50-7.75 (5H, m)

APCI-MASS (m/z) : 184 ($M+H^+$)

Preparation 92

A mixture of 3-(bromoacetyl)benzonitrile (38.2 g) and formamide (190 ml) was heated for 30 minutes at 185°C and cooled to room temperature. The mixture was poured into saturated sodium bicarbonate solution (400 ml) and extracted with ethyl acetate (1.8 ℓ). The organic layer was washed with water and brine, dried over magnesium sulfate. After evaporation to 200 ml, the resulting precipitate was collected by filtration, washed with ethyl acetate - isopropyl ether (2:1) to give 3-(imidazol-4-yl)benzonitrile (13.3 g).

mp : 190-191°C

IR (KBr) : 2250-3240 (br), 2224, 1606, 1477, 1333, 1070, 970, 824, 789 cm^{-1}

NMR (DMSO-d_6, δ) : 7.50-7.68 (2H, m), 7.70-7.87 (2H, m), 8.05-8.20 (2H, m), 12.32 (1H, br)

APCI-MASS (m/z) : 170 ($M+H^+$)

Preparation 93

To a solution of methyl 4-formylbenzoate (5.0 g) in ethanol (50 ml) was added sodium borohydride (576 mg) carefully at 0-5°C and stirred for 30 minutes. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give methyl 4-hydroxymethylbenzoate (5.06 g).

IR (KBr) : 2750-3670 (br), 1722, 1614, 1437, 1286, 1111, 1047, 1016, 756 cm^{-1}

NMR ($CDCl_3$, δ) : 1.89 (1H, t, J=5.9Hz), 3.92 (3H, s), 4.77 (2H, d, J=5.9Hz), 7.37-7.50 (2H, m), 7.97-

8.10 (2H, m)

APCI-MASS (m/z) : 167 ($M+H^+$)

Preparation 94

To a solution of methyl 4-hydroxymethylbenzoate (5.0 g) and imidazole (4.1 g) in N,N-dimethylformamide (25 ml) was added tert-butyldimethylsilyl chloride (4.77 g) carefully at 0-5°C and stirred for 2 hours at room temperature. The reaction mixture was poured into 0.1N hydrochloric acid (100 ml) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give methyl 4-(tert-butyldimethylsilyloxymethyl)benzoate (8.43 g).

IR (Neat) : 2954, 2859, 1724, 1464, 1281, 1107, 841 cm^{-1}

NMR ($CDCl_3$, δ) : 0.11 (6H, s), 0.95 (9H, s), 3.91 (3H, s), 4.79 (2H, s), 7.34-7.44 (2H, m), 7.95-8.05 (2H, m)

APCI-MASS (m/z) : 281 ($M+H^+$)

Preparation 95

A mixture of methyl 4-(tert-butyldimethylsilyloxymethyl)benzoate (1.0 g) and hydrazine monohydrate (0.87 ml) in ethanol (0.8 ml) was refluxed for one hour. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give [4-(tert-butyldimethylsilyloxymethyl)benzoyl]hydrazine (1.0 g).

mp : 83-85°C

IR (KBr) : 3273 (br), 2954, 2858, 1662, 1599, 1539, 1335, 1254, 1093, 841 cm^{-1}

NMR (DMSO-d_6, δ) : 0.08 (6H, s), 0.91 (9H, s), 4.47 (2H, s), 4.75 (2H, s), 7.30-7.40 (2H, m), 7.75-

7.85 (2H, m), 9.72 (1H, s)

APCI-MASS (m/z) : 281 ($M+H^+$)

Preparation 96

To a mixture of [4-(tert-butyldimethylsilyloxymethyl)-benzoyl]hydrazine (8.0 g) and ethyl acetimidate·hydrochloride (4.24 g) in ethanol (160 ml) was added triethylamine (4.8 ml) at room temperature and stirred for 30 minutes. The reaction mixture was evaporated in vacuo. Then the residue was dissolved in ethyl acetate (120 ml), washed with water and brine. The organic layer was dried over magnesium sulfate, evaporated in vacuo. And the residue was heated for 10 minutes at 200°C, cooled to room temperature, chromatographed on silica gel (200 g, eluting with n-hexane - ethyl acetate (2:1)) to give 2-[4-(tert-butyldimethylsilyloxymethyl)-phenyl]-5-methyl-1,3,4-oxadiazole (6.35 g).

mp : 62-65°C

IR (KBr) : 2956, 2933, 2897, 2860, 1576, 1502, 1257, 1086, 843 cm^{-1}

NMR (DMSO-d_6, δ) : 0.10 (6H, s), 0.92 (9H, s), 2.58 (3H, s), 4.80 (2H, s), 7.45-7.55 (2H, m), 7.90-8.00 (2H, m)

APCI-MASS (m/z) : 305 ($M+H^+$)

Preparation 97

To a solution of 2-[4-(tert-butyldimethylsilyloxy-methyl)phenyl]-5-methyl-1,3,4-oxadiazole (2.0 g) in methanol (20 ml) was added 1N hydrochloric acid (13 ml) dropwise at 0-5°C and stirred for one hour. The reaction mixture was recooled to 0-5°C, and sodium bicarbonate (1.15 g) was added thereto carefully. The mixture was extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The resulting precipitate was collected by filtration and washed with

n-hexane to give 2-(4-hydroxymethylphenyl)-5-methyl-(1,3,4-oxadiazole (0.75 g).

IR (KBr) : 3323 (br), 2877, 2819, 1614, 1576, 1416, 1257, 1053, 833, 729 cm^{-1}

NMR (DMSO-d_6, δ) : 2.58 (3H, s), 4.59 (2H, d, J=5.4Hz), 5.39 (1H, t, J=5.4Hz), 7.47-7.57 (2H, m), 7.87-7.97 (2H, m)

APCI-MASS (m/z) : 191 ($M+H^+$)

Preparation 98

A mixture of 2-[4-(tert-butyldimethylsilyloxymethyl)-phenyl]-5-methyl-1,3,4-oxadiazole (5.05 g) and benzylamine (18 ml) was heated for 2 drops at 150°C. After cooling to room temperature, the mixture was chromatographed on silica gel (250 g, eluting with dichloromethane-methanol (20:1)) to give 4-benzyl-3-[4-(tert-butyldimethylsilyloxymethyl)-phenyl]-5-methyl-4H-1,2,4-triazole (5.04 g).

mp : 90-91°C

IR (KBr) : 2953, 2929, 2885, 2854, 1524, 1460, 1431, 1255, 1101, 1003, 835 cm^{-1}

NMR ($CDCl_3$, δ) : 0.08 (6H, s), 0.94 (9H, s), 2.37 (3H, s), 4.77 (2H, s), 5.16 (2H, s), 6.90-7.03 (2H, m), 7.27-7.55 (7H, m)

APCI-MASS (m/z) : 394 ($M+H^+$)

Preparation 99

To the solution of N-cycloheptyl-4-(4-benzyl-5-methyl-4H-1,2,4-triazol-3-yl)benzylamine (500 mg) in methanol (25 ml) was added Palladium Black (500 mg) and formic acid (1.25 ml). The mixture was stirred for 4.5 hours at the room temperature. Palladium Black was removed by filtration. The filtrate was basified with 1N sodium hydroxide aqueous solution under ice cooling and evaporated in vacuo to dryness. The residue was diluted with dichloromethane-methanol (5:1), dried over magnesium

sulfate, evaporated in vacuo. After chromatography on silica gel (15 g, eluting with dichloromethane-methanol (4:1)) N-cycloheptyl-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzylamine (219.6 mg) was isolated.

IR (KBr) : 2500-3700 (br), 2926, 2854, 1564, 1458, 1099 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.00 (12H, m), 2.48 (3H, s), 2.65-2.80 (1H, m), 3.83 (2H, s), 4.60-5.15 (2H, br), 7.30-7.40 (2H, m), 7.90-8.00 (2H, m)

APCI-MASS (m/z) : 285 ($M+H^+$)

Preparation 100

To the solution of 3-(1H-tetrazol-5-yl)benzaldehyde (600 mg) in N,N-dimethylformamide (6 ml) was added sodium hydride (60% oil suspension, 138 mg) at 0-5°C. After stirring for 15 minutes, to the mixture was added methyl iodide (0.43 ml). The solution was stirred for 3 hours at room temperature, then stirred for 30 minutes at 40°C. The reaction mixture was poured into water and extracted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. After chromatography on silica gel (25 g, eluting with n-hexane - ethyl acetate (1:1), 3-(2-methyl-2H-tetrazol-5-yl)benzaldehyde (510.7 mg) and 3-(1-methyl-1H-tetrazol-5-yl)benzaldehyde (81.6 mg) was obtained.

3-(2-Methyl-2H-tetrazol-5-yl)benzaldehyde

mp : 98-99°C

IR (KBr) : 3072, 2839, 1691, 1587, 1520, 1443 cm^{-1}

NMR (DMSO-d_6, δ) : 4.47 (3H, s), 7.81 (1H, dd, J=7.7, 7.7Hz), 8.05-8.10 (1H, m), 8.33-8.40 (1H, m), 8.55-8.58 (1H, m), 10.14 (1H, s)

APCI-MASS (m/z) : 189 ($M+H^+$)

3-(1-Methyl-1H-tetrazol-5-yl)benzaldehyde

IR (KBr) : 1699, 1608, 1535, 1450, 1394 cm^{-1}

NMR (DMSO-d_6, δ) : 4.22 (3H, s), 7.87 (1H, dd, J=7.7, 7.7Hz), 8.13-8.25 (2H, m), 8.38-8.40 (1H, m), 10.14 (1H, s)

APCI-MASS (m/z) : 189 ($M+H^+$)

Preparation 101

To the solution of 4-fluorobenzaldehyde (3.0 g) and 1H-1,2,4-triazole (2.0 g) in N,N-dimethylformamide (30 ml) was added potassium carbonate (4.0 g). Then the mixture was heated for one hour at 120°C. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The resulting solid was collected and washed with diisopropyl ether to give 4-(1H-1,2,4-triazol-1-yl)benzaldehyde (1.95 g).

mp : 147-148°C

IR (KBr) : 3130, 2856, 1709, 1603, 1518, 1441, 1275 cm^{-1}

NMR ($CDCl_3$, δ) : 7.88-8.01 (2H, m), 8.01-8.14 (2H, m), 8.16 (1H, s), 8.70 (1H, s), 10.07 (1H, s)

APCI-MASS (m/z) : 174 ($M+H^+$)

Preparation 102

To a solution of 4-fluorobenzaldehyde (5.0 g) and 1H-1,2,3-triazole (3.33 g) in N,N-dimethylformamide (50 ml) was added potassium carbonate (6.68 g). Then the mixture was heated for one hour at 120°C. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml), washed with water, brine, dried over magnesium sulfate and evaporated to about 50 ml in vacuo. The resulting precipitate was collected by filtration, washed with n-hexane to give 4-(1H-1,2,3-triazol-1-yl)benzaldehyde (3.44 g). The mother liquid was evaporated to about 10 ml in vacuo. The resulting precipitate was also collected in the

similar procedure as mentioned above to give 4-(2H-1,2,3-triazol-2-yl)benzaldehyde (297 mg).

4-(1H-1,2,3-Triazol-1-yl)benzaldehyde

IR (KBr) : 3138, 3116, 2845, 1695, 1603, 1516, 1419, 1389 cm^{-1}

NMR ($CDCl_3$, δ) : 7.91 (1H, s), 7.93-8.11 (4H, m), 8.12 (1H, s), 10.09 (1H, s)

APCI-MASS (m/z) : 174 ($M+H^+$)

4-(2H-1,2,3-Triazol-2-yl)benzaldehyde

IR (KBr) : 3114, 3084, 2715, 1699, 1603, 1508, 1408, 1383 cm^{-1}

NMR ($CDCl_3$, δ) : 7.89 (2H, s), 7.95-8.06 (2H, m), 8.23-8.33 (2H, m), 10.06 (1H, s)

APCI-MASS (m/z) : 174 ($M+H^+$)

Preparation 103

To a solution of 4-fluorobenzaldehyde (6.21 g) in N,N-dimethylformamide (100 ml) were added 1-methylpiperazine (6.01 g) and powdered potassium carbonate (8.29 g), and the mixture was stirred at 150°C for 4.5 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(4-methylpiperazin-1-yl)benzaldehyde (5.31 g) as a yellow solid.

IR (KBr) : 2935, 2840, 2790, 2750, 1690, 1600, 1560, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.4-2.5 (4H, m), 3.35-3.45 (4H, m), 7.04 (2H, d, J=8.8Hz), 7.70 (2H, d, J=8.8Hz), 9.71 (1H, s)

Preparation 104

To a solution of 4-bromoaniline (6.88 g) in pyridine (20 ml) was added dropwise methanesulfonyl chloride (4.58 g) at 5°C and the mixture was stirred at 5°C for 1.5 hours and at room temperature for 1.5 hours. The mixture was poured into a mixture of ethyl acetate and dilute hydrochloric acid and the insoluble materials were filtered off. The filtrate was separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized and the crystal was collected by filtration, washed with diisopropyl ether and dried to give 4-bromo-N-methylsulfonylaniline (8.30 g).

IR (KBr) : 3290, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00 (3H, s), 7.16 (2H, d, J=8.7Hz), 7.52 (2H, d, J=8.7Hz), 9.92 (1H, br)

Preparation 105

To a suspension of N-methyl-N-methoxy-4-sulfamoylbenzamide (3.53 g) and benzoic acid (1.95 g) in dichloromethane (100 ml) were added 4-dimethylaminopyridine (1.96 g) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide·hydrochloride (3.07 g) at room temperature and the mixture was stirred at the same temperature for 18 hours. The mixture was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-methyl-N-methoxy 4-(N-benzoylsulfamoyl)benzamide (1.35 g).

IR (KBr) : 3072, 2970, 2937, 1649, 1597, 1560, 1544 cm^{-1}

NMR (DMSO-d_6, δ) : 3.27 (3H, s), 3.55 (3H, s), 7.35-7.5 (3H, m), 7.68 (2H, d, J=8.2Hz), 7.85-7.95 (2H, m), 7.96 (2H, d, J=8.2Hz)

APCI-MASS (m/z) : 349 ($M+H^+$)

Preparation 106

To a suspension of 4-cyanobenzaldehyde (26.23 g) was added carefully sodium borohydride (3.78 g) at room temperature, and the mixture was stirred at the same temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo to give crude 4-cyanobenzyl alcohol (24.97 g) as an oil.

IR (Film) : 3419, 2916, 2875, 2229, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 2.07 (1H, br), 4.79 (2H, br s), 7.48 (2H, d, J=8.1Hz), 7.65 (2H, d, J=8.1Hz)

APCI-MASS (m/z) : 134 ($M+H^+$)

Preparation 107

To a solution of 4-cyanobenzyl alcohol (24.96 g) in N,N-dimethylformamide (100 ml) were added imidazole (16.0 g) and tert-butyldimethylsilyl chloride (31.0 g) at room temperature and the mixture was stirred for 2 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(tert-butyldimethylsilyloxymethyl)benzonitrile (40.78 g) as an oil.

IR (Film) : 2954, 2429, 2885, 2858, 2229, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 0.11 (6H, s), 0.95 (9H, s), 4.79 (2H, s), 7.43 (2H, d, J=8.3Hz), 7.63 (2H, d, J=8.3Hz)

APCI-MASS (m/z) : 248 ($M+H^+$)

Preparation 108

To a solution of n-butyllithium (1.71M hexane solution, 58.5 ml) in diethyl ether (150 ml) was added

dropwise 3-bromopyridine (15.8 g) at 5°C, and the mixture was stirred at 5°C for an hour. The mixture was cooled to -60°C and a solution of 4-(tert-butyldimethylsilyloxymethyl)benzonitrile (19.79 g) in diethyl ether (80 ml) was added dropwise over 1.2 hours under nitrogen. The mixture was gradually warmed to room temperature and stirred at the same temperature for additional 2 hours. The mixture was poured into a mixture of ethyl acetate and dilute hydrochloric acid, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-[(4-tert-butyldimethylsilyloxymethyl)benzoyl]pyridine (4.96 g) as a red oil.

IR (Film) : 3034, 2954, 2930, 2895, 2856, 1660, 1608, 1585, 1537 cm^{-1}

NMR ($CDCl_3$, δ) : 0.16 (6H, s), 0.99 (9H, s), 4.87 (2H, s), 7.50 (2H, d, J=7.6Hz), 7.83 (2H, d, J=7.6Hz), 7.4-7.5 (1H, m), 8.1-8.2 (1H, m), 8.8-8.9 (1H, m), 8.99 (1H, d, J=2.1Hz)

APCI-MASS (m/z) :328 ($M+H^+$)

Preparation 109

To a suspension of 3-[(4-tert-butyldimethylsilyloxymethyl)benzoyl]pyridine (4.94 g) in ethylene glycol (40 ml) were added potassium hydroxide (1.27 g) and hydrazine hydrate (4.84 g) and the mixture was stirred at 150°C for 2 hours and at 200°C for 4 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(3-pyridylmethyl)benzyl alcohol (1.26 g) as an orange oil.

IR (Film) : 3323, 3030, 2920, 2868, 1579, 1549,

1514 cm^{-1}

NMR ($CDCl_3$, δ) : 1.85 (1H, br), 3.97 (2H, s), 4.67 (2H, s), 7.15-7.5 (6H, m), 8.45-8.55 (2H, m)

APCI-MASS (m/z) : 200 ($M+H^+$)

Preparation 110

To a solution of 4-(3-pyridylmethyl)benzyl alcohol (1.26 g) in chloroform (30 ml) was activated manganese dioxide (5.50 g) and the mixture was refluxed for 2 hours. Manganese dioxide was removed off and the filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 4-(3-pyridylmethyl)-benzaldehyde (1.09 g) as an orange oil.

IR (Film) : 3029, 2989, 2910, 2831, 2738, 1697, 1599, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 4.07 (2H, s), 7.24 (1H, dd, J=7.8, 4.8Hz), 7.35 (2H, d, J=8.1Hz), 7.47 (1H, dd, J=7.8, 1.4Hz), 7.83 (2H, d, J=8.1Hz), 8.49 (1H, d, J=1.4Hz), 8.51 (1H, s), 9.99 (1H, s)

APCI-MASS (m/z) : 198 ($M+H^+$)

Preparation 111

To a solution of 1-ethoxycarbonyl-4-diethylphosphono-1,4-dihydropyridine (34.71 g) in tetrahydrofuran (200 ml) was added dropwise n-butyllithium (1.71M hexane solution, 70.2 ml) at -60°C over 30 minutes under nitrogen, and the mixture was stirred at -60°C for 40 minutes. To this solution was added dropwise a solution of 4-cyanobenzyl bromide (27.40 g) in tetrahydrofuran (80 ml) at -60°C and the mixture was gradually warmed to room temperature and stirred for 21 hours. The mixture was poured into a mixture of ethyl acetate and dilute hydrochloric acid, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on

silica gel to give 1-ethoxycarbonyl-4-(4-cyanobenzyl)-4-diethylphosphono-1,4-dihydropyridine (47.10 g) as a crude red oil.

IR (Film) : 3053, 2891, 2933, 2908, 2227, 1728, 1689, 1626, 1606 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.4 (9H, m), 3.06 (2H, d, J=7.6Hz), 4.1-4.3 (6H, m), 4.7-4.9 (2H, m), 7.65-7.9 (2H, m), 7.22 (2H, d, J=8.2Hz), 7.55 (2H, d, J=8.2Hz)

APCI-MASS (m/z) : 405 ($M+H^+$)

Preparation 112

To a solution of 1-ethoxycarbonyl-4-(4-cyanobenzyl)-4-diethylphosphono-1,4-dihydropyridine (42.10 g) in dichloromethane (350 ml) was added dropwise diisobutylaluminum hydride (1.01M toluene solution, 515 ml) at -60°C over 55 minutes and the mixture was stirred at -60°C for 1.5 hours. The mixture was gradually warmed to 5°C and stirred at 5°C for 1.5 hours. To the mixture were added sodium fluoride (87.34 g) and water (28.11 g) and the mixture was stirred at room temperature for an hour. The insoluble materials were filtered off and washed with dichloromethane. The filtrate was evaporated in vacuo and the residue was dissolved in tetrahydrofuran (200 ml). To this solution was added 6N hydrochloric acid (30 ml) and the mixture was stirred at room temperature for 3 hours. The mixture was adjusted to pH ca. 8 by addition of 5N sodium hydroxide and extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(4-pyridylmethyl)benzaldehyde (4.62 g) as a red oil.

IR (Film) : 3381, 3053, 3030, 2924, 2831, 2738, 1697, 1606, 1576 cm^{-1}

NMR ($CDCl_3$, δ) : 4.08 (2H, s), 7.1-7.2 (2H, m),

7.3-7.45 (2H, m), 7.8-7.9 (2H, m), 8.5-8.6 (2H, m), 10.00 (1H, s)

Preparation 113

To a solution of pyrazole (1.67 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60% oil suspension, 950 mg) at 0-5°C. After stirring for 30 minutes, to the mixture was added a solution of 4-bromomethylbenzonitrile (4.0 g) in N,N-dimethylformamide (10 ml) dropwise under ice cooling, and the mixture was stirred for two hours at room temperature. The reaction mixture was diluted with ethyl acetate (240 ml), washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (100 g, eluting with n-hexane - ethyl acetate (1:1)) to give 4-(pyrazol-1-ylmethyl)benzonitrile (3.49 g).

mp : 80-81°C

IR (KBr) : 3055, 2958, 2229, 1610, 1510, 1446, 1392, 1275 cm^{-1}

NMR ($CDCl_3$, δ) : 5.39 (2H, s), 6.33 (1H, dd, J=2.1, 2.1Hz), 7.18-7.30 (2H, m), 7.44 (1H, d, J=2.1Hz), 7.55-7.70 (3H, m)

APCI-MASS (m/z) : 184 ($M+H^+$)

Preparation 114

To a solution of imidazole (1.67 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60% oil suspension, 950 mg) at 0-5°C. After stirring for 30 minutes, to the mixture was added a solution of 4-bromomethylbenzonitrile (4.0 g) in N,N-dimethylformamide (10 ml) dropwise under ice cooling, and the mixture was stirred for two hours at room temperature. The reaction mixture was diluted with ethyl acetate (240 ml), washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on

silica gel (100 g, eluting with dichloromethane - methanol (15:1)) to give 4-(imidazol-1-ylmethyl)benzonitrile (3.26 g).

IR (KBr) : 3095, 3057, 2229, 1608, 1510, 1425, 1236, 1074, 731 cm^{-1}

NMR ($CDCl_3$, δ) : 5.21 (2H, s), 6.90 (1H, s), 7.14 (1H, s), 7.15-7.27 (2H, m), 7.57 (1H, s), 7.60-7.72 (2H, m)

APCI-MASS (m/z) : 184 ($M+H^+$)

Preparation 115

To a suspension of 3,5-di-tert-butyl-4-hydroxybenzoic acid (10.0 g) in methanol (100 ml) were added sodium hydroxide (1.6 g) and water (6 ml) and the mixture was stirred at room temperature for 35 minutes. The mixture was evaporated in vacuo and dried thoroughly. The sodium salt was suspended in petroleum ether (60 ml), and thionyl chloride (30.93 g) was added thereto and the mixture was stirred at room temperature for 16 hours. The mixture was evaporated in vacuo and the residue was redissolved in petroleum ether (200 ml). The insoluble materials were filtered off and the filtrate was evaporated in vacuo to give 3,5-di-tert-butyl-4-hydroxybenzoyl chloride (9.81 g) as a yellow solid.

IR (KBr) : 3554, 2974, 2956, 1736, 1597, 1574 cm^{-1}

Preparation 116

To a solution of sodium azide (4.61 g) in water (30 ml) was added dropwise a solution of 3,5-di-tert-butyl-4-hydroxybenzoyl chloride (12.72 g) in tetrahydrofuran (60 ml) at 5°C over 30 minutes, and the mixture was stirred at 5°C for 1.5 hours. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. To the residue was added n-hexane (60 ml) and the insoluble

materials were filtered off. The filtrate was evaporated in vacuo to give 3,5-di-tert-butyl-4-hydroxybenzoyl azide (1.49 g) as a yellow solid.

IR (KBr) : 3593, 2966, 2912, 2873, 2141, 1668, 1599 cm^{-1}

Preparation 117

A suspension of 3,5-di-tert-butyl-4-hydroxybenzoyl azide (1.49 g) in benzene (30 ml) was refluxed for an hour under nitrogen. To the mixture was added tert-butanol (4.01 g) and the mixture was refluxed for 3 hours. The mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give N-tert-butoxycarbonyl-3,5-di-tert-butyl-4-hydroxyaniline (1.17 g) as a white solid.

IR (KBr) : 3647, 3331, 2958, 2913, 2873, 1693, 1606, 1547 cm^{-1}

NMR (DMSO-d_6, δ) : 1.34 (18H, s), 1.44 (9H, s), 6.60 (1H, s), 7.22 (2H, s), 8.84 (1H, br s)

Preparation 118

To a solution of N-tert-butoxycarbonyl-3,5-di-tert-butyl-4-hydroxyaniline (3.97 g) in ethyl acetate (60 ml) and ethanol (15 ml) was added 4N hydrochloric acid in ethyl acetate (30.8 ml) and the mixture was stirred at room temperature for 24 hours. The mixture was evaporated in vacuo and the residue was triturated with diisopropyl ether. The powder was collected by filtration, washed with diisopropyl ether and dried in vacuo to give 3,5-di-tert-butyl-4-hydroxyaniline·hydrochloride (2.85 g).

IR (KBr) : 2966, 2912, 2873, 2590, 1581, 1512 cm^{-1}

NMR (DMSO-d_6, δ) : 1.38 (18H, s), 7.12 (2H, s), 7.34 (1H, s), 9.83 (2H, br s)

Preparation 119

To a suspension of 4-formylbenzoic acid (1.65 g), 3,5-di-tert-butyl-4-hydroxyaniline·hydrochloride (2.83 g) and 1-hydroxybenzotriazole (1.49 g) in dichloromethane (60 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (1.71 g) at room temperature and the resulting solution was stirred at the same temperature for 20 hours. The mixture was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-[(3,5-di-tert-butyl-4-hydroxyphenyl)carbamoyl]benzaldehyde (2.53 g).

IR (KBr) : 3624, 3286, 2958, 2912, 2872, 1703, 1645, 1606, 1547 cm^{-1}

NMR (DMSO-d_6, δ) : 1.43 (18H, s), 6.83 (2H, d, J=5.1Hz), 7.09 (2H, d, J=5.1Hz), 7.12 (2H, s), 10.07 (1H, s), 10.19 (1H, s)

APCI-MASS (m/z) : 354 ($M+H^+$)

Preparation 120

To a suspension of 4-formylbenzoic acid (7.5 g) in dichloromethane (25 ml) were added thionyl chloride (11.9 g) and N,N-dimethylformamide (365 mg) at room temperature, and the mixture was refluxed for 4 hours under nitrogen. The mixture was evaporated in vacuo and dried in vacuo to give crude 4-formylbenzoyl chloride (8.53 g) as a white powder.

IR (KBr) : 3066, 2856, 1745, 1691, 1576, 1504 cm^{-1}

Preparation 121

To a solution of 4-fluoroaniline (5.0 g) and triethylamine (6.07 g) in dichloromethane (60 ml) was added portionwise 4-formylbenzoyl chloride (8.53 g) at 5°C and the mixture was stirred at room temperature for 2 hours. The mixture was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was

crystallized from hexane - ethyl acetate (3:1) and collected by filtration, washed with hexane - ethyl acetate (3:1) and dried in vacuo to give 4-[N-(4-fluorophenyl)-carbamoyl]benzaldehyde (4.58 g).

IR (KBr) : 3356, 2872, 1703, 1651, 1606, 1537, 1514 cm^{-1}

NMR (DMSO-d_6, δ) : 7.15-7.3 (2H, m), 7.8-7.9 (2H, m), 8.06 (2H, d, J=8.4Hz), 8.14 (2H, d, J=8.4Hz), 10.12 (1H, s), 10.53 (1H, br s)

APCI-MASS (m/z) : 244 ($M+H^+$)

Preparation 122

To a suspension of sodium hydride (60% oil dispersion, 464 mg) in N,N-dimethylformamide (50 ml) was added dropwise a solution of 4-[N-(4-fluorophenyl)carbamoyl]benzaldehyde (2.63 g) in N,N-dimethylformamide (40 ml) at 5°C under nitrogen, and the mixture was stirred at room temperature for an hour. To the mixture was added methyl iodide (3.29 g), and the mixture was stirred at room temperature for 3 hours. The mixture was poured into a mixture of ethyl acetate and ice water. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-[N-(4-fluorophenyl)-N-methylcarbamoyl]benzaldehyde (2.24 g) as an orange oil.

IR (Film) : 3068, 2981, 2939, 2839, 2737, 1703, 1639, 1608, 1571, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.37 (3H, s), 7.05-7.2 (2H, m), 7.25-7.35 (2H, m), 7.46 (2H, d, J=8.1Hz), 7.77 (2H, d, J=8.1Hz), 9.93 (1H, s)

APCI-MASS (m/z) : 258 ($M+H^+$)

Preparation 123

To a solution of 1,4-bis(hydroxymethyl)benzene (25.72

g) in N,N-dimethylformamide (300 ml) were added imidazole (15.21 g) and tert-butyldimethylsilyl chloride (28.06 g) at room temperature, and the mixture was stirred for 10 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(tert-butyldimethylsilyloxymethyl)benzyl alcohol (27.89 g) as an oil.

IR (Film) : 3352, 2954, 2931, 2887, 2858, 1541, 1514, 1466 cm^{-1}

NMR (DMSO-d_6, δ) : 0.07 (6H, s), 0.90 (9H, s), 4.47 (2H, d, J=5.7Hz), 4.68 (2H, s), 5.10 (1H, t, J=5.7Hz), 7.2-7.3 (4H, m)

Preparation 124

To a solution of 4-(tert-butyldimethylsilyloxymethyl)-benzyl alcohol (27.86 g) in chloroform (300 ml) was added activated manganese dioxide (47.98 g) and the mixture was refluxed for 3.5 hours. Manganese dioxide was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(tert-butyldimethylsilyloxymethyl)benzaldehyde (26.86 g) as a pale yellow oil.

IR (Film) : 2955, 2931, 2889, 2858, 2731, 1703, 1608, 1578, 1541 cm^{-1}

NMR (DMSO-d_6, δ) : 0.10 (6H, s), 0.92 (9H, s), 4.82 (2H, s), 7.53 (2H, d, J=8.2Hz), 7.89 (2H, d, J=8.2Hz), 9.99 (1H, s)

Preparation 125

To a solution of N-cycloheptyl-4-(tert-butyldimethylsilyloxymethyl)benzylamine (53.74 g) in methanol (250 ml) was added dropwise conc. hydrochloric

acid (38.6 ml) at 5°C, and the mixture was stirred at room temperature for 3 hours. The mixture was evaporated in vacuo and the residue was pulverized with tetrahydrofuran and ethyl acetate. The powder was collected by filtration, washed with ethyl acetate and tetrahydrofuran and ethyl acetate (1:1), and dried in vacuo under phosphorus pentoxide to give N-cycloheptyl-4-hydroxymethylbenzylamine·hydrochloride (37.92 g).

IR (KBr) : 3294, 2927, 2858, 2791, 1578, 1541, 1514, 1456 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-2.2 (12H, m), 3.05-3.25 (1H, m), 4.12 (2H, s), 4.52 (2H, d, J=5.7Hz), 5.27 (1H, t, J=5.7Hz), 7.36 (2H, d, J=8.0Hz), 7.48 (2H, d, J=8.0Hz), 8.7-8.9 (1H, br)

APCI-MASS (m/z) : 234 ($M+H^+$-HCl)

Preparation 126

To a suspension of N-cycloheptyl-4-hydroxymethylbenzylamine·hydrochloride (37.9 g) in chloroform (400 ml) were added activated manganese dioxide (60.86 g) and triethylamine (14.21 g), and the mixture was refluxed for 4 hours. Manganese dioxide was filtered off and the filtrate was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cycloheptyl-4-formylbenzylamine (18.27 g) as a yellow oil.

IR (Film) : 3051, 2924, 2854, 2731, 1701, 1606, 1576, 1468 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.0-2.2 (1H, br), 2.5-2.7 (1H, m), 3.77 (2H, s), 7.56 (2H, d, J=8.1Hz), 7.85 (2H, d, J=8.1Hz), 9.97 (1H, s)

APCI-MASS (m/z) : 232 ($M+H^+$)

Preparation 127

To a solution of N-cycloheptyl-4-formylbenzylamine (18.26 g) in ethanol (200 ml) were added thiazolidin 2,4-dione (9.25 g) and piperidine (6.72 g), and the mixture was refluxed for 17 hours. The mixture was cooled to 5°C and the precipitates were collected by filtration, washed with ethanol and diisopropyl ether and dried in vacuo to give N-cycloheptyl-4-[(2,4-dioxothiazolidin-5-ylidene)methyl]-benzylamine (9.61 g) as a yellow crystal. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give the second crop (4.13 g).

IR (KBr) : 3429, 3024, 2929, 2858, 1684, 1622, 1576, 1547, 1458 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-2.2 (12H, m), 3.05-3.25 (1H, m), 4.12 (2H, s), 7.35 (1H, s), 7.52 (2H, d, J=8.5Hz), 7.58 (2H, d, J=8.5Hz)

APCI-MASS (m/z) : 331 ($M+H^+$)

Preparation 128

To a suspension of N-cycloheptyl-4-[(2,4-dioxothiazolin-5-ylidene)methyl]benzylamine (13.61 g) in tetrahydrofuran (300 ml) and methanol (300 ml) was added 5% sodium-amalgam (56.8 g), and the mixture was stirred at room temperature for 24 hours. The insoluble materials were removed by filtration on celite and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cycloheptyl-4-[(2,4-dioxothiazolidin-5-yl)methyl]benzylamine (5.84 g) as a yellow solid.

IR (KBr) : 3028, 2933, 2862, 2764, 1674, 1630, 1581, 1460 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-2.2 (12H, m), 2.9-3.1 (1H, m), 2.95 (1H, dd, J=13.8, 9.3Hz), 3.36 (1H, dd, J=9.3, 4.0Hz), 4.54 (1H, dd, J=9.3, 4.0Hz), 7.25

(1H, d, J=8.1Hz), 7.38 (1H, d, J=8.1Hz)
APCI-MASS (m/z) : 333 ($M+H^+$)

Preparation 129

To a solution of 4-fluorobenzaldehyde (20.11 g) and 4-chlorophenol (25.0 g) in N,N-dimethylformamide (250 ml) was added powdered potassium carbonate (26.81 g), and the mixture was stirred at 150°C under nitrogen for 7 hours. The mixture was cooled and poured into a mixture of ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(4-chlorophenoxy)benzaldehyde (32.49 g) as a yellow oil.

IR (Film) : 3070, 2985, 2830, 2740, 1735, 1695, 1605, 1580, 1485 cm^{-1}
NMR ($CDCl_3$, δ) : 7.0-7.15 (4H, m), 7.35-7.45 (2H, m), 7.8-7.9 (2H, m), 9.93 (1H, s)
APCI-MASS (m/z) : 235, 233 ($M+H^+$)

Preparation 130

To a solution of 4-fluorobenzaldehyde (5 g) and 3-fluorophenol (5.42 g) in N,N-dimethylformamide (50 ml) was added potassium carbonate (6.68 g). Then the mixture was heated for 3.5 hours at 150°C. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (200 g, eluting with n-hexane - ethyl acetate (10:1)) to give 4-(3-fluorophenoxy)benzaldehyde (8.67 g).

IR (Neat) : 3072, 2831, 2738, 1697, 1587, 1483 cm^{-1}
NMR ($CDCl_3$, δ) : 6.75-7.00 (3H, m), 7.05-7.18 (2H, m), 7.28-7.42 (1H, m), 7.82-7.95 (2H, m), 9.95 (1H, s)
APCI-MASS (m/z) : 217 ($M+H^+$)

Preparation 131

To a solution of 4-fluorobenzaldehyde (3 g) and 4-trifluoromethylphenol (4.7 g) in N,N-dimethylformamide (30 ml) was added potassium carbonate (4.0 g). Then the mixture was heated for 5 hours at 150°C. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (200 g, eluting with n-hexane - ethyl acetate (15:1)) to give 4-(4-trifluoromethylphenoxy)benzaldehyde (982.1 mg).

IR (Neat) : 3074, 2831, 2738, 1701, 1587, 1502 cm^{-1}

NMR ($CDCl_3$, δ) : 7.05-7.25 (4H, m), 7.60-7.75 (2H, m), 7.85-7.98 (2H, m), 9.96 (1H, s)

FAB-MASS (m/z) : 267 ($M+H^+$)

Preparation 132

To a solution of 4-fluorobenzaldehyde (3 g) and 3,4-methylenedioxyphenol (4 g) in N,N-dimethylformamide (30 ml) was added potassium carbonate (4 g). Then the mixture was heated for 2 hours at 150°C. After cooling, the reaction mixture was diluted with ethyl acetate (200 ml), washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (120 g, eluting with n-hexane - ethyl acetate (5:1)) to give 4-(3,4-methylenedioxyphenoxy)benzaldehyde (2.67 g).

mp : 65-66°C

IR (KBr) : 1691, 1600, 1481, 1227 cm^{-1}

NMR ($CDCl_3$, δ) : 6.02 (2H, s), 6.50-6.65 (2H, m), 6.82 (1H, d, J=8.3Hz), 6.96-7.07 (2H, m), 7.78-7.89 (2H, m), 9.91 (1H, s)

APCI-MASS (m/z) : 243 ($M+H^+$)

Preparation 133

To a solution of 4-fluorobenzaldehyde (2.48 g) and 3,5-di-tert-butyl-4-methoxymethoxyphenol (5.33 g) in N,N-dimethylformamide (40 ml) was added powdered potassium carbonate (2.76 g), and the mixture was stirred at 150°C for 6 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(3,5-di-tert-butyl-4-methoxymethoxyphenoxy)benzaldehyde (4.03 g) as an orange oil.

IR (Film) : 2960, 2872, 2740, 2693, 1581, 1504 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (18H, s), 3.66 (3H, s), 4.94 (2H, s), 6.99 (2H, s), 7.02 (2H, d, J=8.8Hz), 7.83 (2H, d, J=8.8Hz), 9.92 (1H, s)

APCI-MASS (m/z) : 371 ($M+H^+$)

Preparation 134

To a solution of 4-fluoronitrobenzene (14.11 g) and 4-fluorophenol (12.33 g) in N,N-dimethylformamide (150 ml) was added powdered potassium carbonate (15.20 g), and the mixture was stirred at 100°C for 4.5 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized and the crystal was collected by filtration and washed with hexane and dried to give 4-(4-fluorophenoxy)nitrobenzene (22.96 g) as a yellow crystal.

IR (KBr) : 3110, 3075, 2925, 2835, 1585, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 6.95-7.2 (6H, m), 8.15-8.3 (2H, m)

APCI-MASS (m/z) : 234 ($M+H^+$)

Preparation 135

To a suspension of 3-hydroxybenzyl alcohol (12.41 g) and 1-chloro-4-fluorobenzene (19.58 g) in 1,3-dimethyl-2-imidazolidinone (40 ml) were added powdered potassium carbonate (8.29 g), cuprous chloride (198 mg) and 8-hydroxyquinoline (290 mg) at room temperature, and the mixture was stirred at 150°C for 8 hours. The mixture was poured into a mixture of ethyl acetate and ice water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(4-fluorophenoxy)benzyl alcohol (3.98 g) as a yellow oil.

IR (Film) : 3352, 3074, 2931, 2875, 1610, 1585, 1502, 1448 cm^{-1}

NMR (DMSO-d_6, δ) : 4.47 (2H, d, J=5.6Hz), 5.22 (1H, t, J=5.6Hz), 6.8-7.4 (8H, m)

Preparation 136

To a solution of 4-fluorobenzonitrile (50.0 g) and 4-fluorophenol (50.93 g) in N,N-dimethylformamide (400 ml) was added powdered potassium carbonate (62.75 g), and the mixture was stirred at 150°C for 6 hours. The mixture was cooled to 5°C and poured into ice water (2.5 ℓ). The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-(4-fluorophenoxy)-benzonitrile (87.56 g).

IR (KBr) : 3188, 3076, 2220, 1649, 1608, 1483 cm^{-1}

NMR (DMSO-d_6, δ) : 7.05-7.15 (2H, m), 7.2-7.45 (4H, m), 7.8-7.9 (2H, m)

APCI-MASS (m/z) : 214 ($M+H^+$)

Preparation 137

To a stirred suspension of 3-acetylbenzonitrile (25.4 g) in ethyl ether - 1,4-dioxane (10:1, 275 ml) was added

bromine (9 ml) dropwise at room temperature. After 40 minutes, to the mixture was added sodium bicarbonate (15 g) in water (200 ml) at 0-5°C, and extracted with ethyl acetate. The organic layer was separated and washed with saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate, evaporated in vacuo to give 3-(bromoacetyl)benzonitrile (39.2 g).

IR (KBr) : 3103, 3068, 2941, 2229, 1707, 1599, 1429, 1279, 1223, 1149 cm^{-1}

NMR ($CDCl_3$, δ) : 4.42 (2H, s), 7.66 (1H, dd, J=8.1, 8.1Hz), 7.85-7.95 (1H, m), 8.18-8.32 (2H, m)

Preparation 138

A mixture of 3-(pyrazol-3-yl)benzaldehyde (56.0 g) and benzylamine (42.6 ml) in toluene (560 ml) was refluxed for 5 hours. The reaction mixture was cooled to room temperature, and evaporated in vacuo. The residue was suspended in ethanol (840 ml) and sodium borohydride (12.3 g) was added carefully under ice cooling. Then the mixture was stirred for one hour at 50°C. After additional stirring for 2 hours at room temperature, the reaction mixture was evaporated in vacuo. To the residue was added water (300 ml), and extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (1.5 kg, eluting with dichloromethane - methanol (10:1)) to give N-benzyl-3-(pyrazol-3-yl)benzylamine (71.8 g).

mp : 82-83°C

IR (KBr) : 2290-3310 (br), 1606, 1543, 1441, 1354 cm^{-1}

NMR (DMSO-d_6, δ) : 3.71 (2H, s), 3.72 (2H, s), 6.68 (1H, d, J=2.1Hz), 7.15-7.42 (7H, m), 7.50-7.90 (3H, m), 12.85, 13.22 (total 1H, each br)

APCI-MASS (m/z) : 264 ($M+H^+$)

Preparation 139

To a solution of 4-(4-fluorophenoxy)aniline (2.03 g) and cycloheptanone (1.35 g) in ethanol (40 ml) were added simultaneously a solution of sodium cyanoborohydride (314 mg) in ethanol (30 ml) and a solution of acetic acid (601 mg) in ethanol (10 ml) over 1 hour at room temperature. The mixture was stirred at room temperature for additional 1.2 hours. The mixture was evaporated in vacuo and the residue was poured into a mixture of ethyl acetate and water and adjusted to pH 8 by addition of 5N sodium hydroxide aqueous solution. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cycloheptyl-4-(4-fluorophenoxy)aniline (2.11 g) as a red oil.

IR (Film) : 3405, 2925, 2855, 1735, 1610, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.15 (12H, m), 3.3-3.5 (1H, m), 6.4-6.6 (2H, m), 6.75-7.05 (6H, m)

APCI-MASS (m/z) : 300 ($M+H^+$)

Preparation 140

The mixture of 4-(4-fluorophenoxy)benzaldehyde (1.73 g) and benzylamine (1.29 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (303 mg) and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-benzyl-[4-(4-fluorophenoxy)]benzylamine (1.78 g) as a yellow oil.

IR (Film) : 3062, 3028, 2916, 2821, 1605, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 3.78 (2H, s), 3.82 (2H, s), 6.9-7.1

(6H, m), 7.2-7.4 (7H, m)

APCI-MASS (m/z) : 308 ($M+H^+$)

Preparation 141

The mixture of 4-(4-fluorophenoxy)benzaldehyde (1.73 g) and pentylamine (1.40 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (303 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-pentyl-4-(4-fluorophenoxy)benzylamine (1.72 g) as a yellow oil.

IR (Film) : 3051, 2956, 2929, 2858, 2818, 1610, 1498 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.4Hz), 1.2-1.4 (4H, m), 1.5-1.7 (2H, m), 2.63 (2H, t, J=7.1Hz), 3.76 (2H, s), 6.9-7.1 (6H, m), 7.28 (2H, d, J=9.1Hz)

APCI-MASS (m/z) : 288 ($M+H^+$)

Preparation 142

The mixture of 4-(4-fluorophenoxy)benzaldehyde (2.16 g) and cyclohexylamine (1.49 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (378 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cyclohexyl-4-(4-

fluorophenoxy)benzylamine (3.06 g) as a yellow oil.

IR (Film) : 3034, 2929, 2852, 1608, 1497 cm^{-1}
NMR ($CDCl_3$, δ) : 1.0-1.4 and 1.5-2.0 (10H, m), 2.4-2.6 (1H, m), 3.78 (2H, s), 6.9-7.1 (6H, m), 7.28 (2H, d, J=8.4Hz)
APCI-MASS (m/z) : 300 ($M+H^+$)

Preparation 143

The mixture of 4-(4-fluorophenoxy)benzaldehyde (2.16 g) and cyclopentylamine (1.28 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (378 mg) and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cyclopentyl 4-(4-fluorophenoxy)benzylamine (2.67 g) as a yellow oil.

IR (Film) : 3032, 2953, 2868, 2819, 1608, 1500 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (8H, m), 3.05-3.25 (1H, m), 3.74 (2H, s), 6.9-7.1 (6H, m), 7.27 (2H, d, J=8.4Hz)
APCI-MASS (m/z) : 286 ($M+H^+$)

Preparation 144

The mixture of 4-(4-fluorophenoxy)benzylamine (4.35 g) and 2,3,5,6-tetrahydro-4H-pyran-4-one (2.40 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (80 ml). To this solution was added carefully sodium borohydride (757 mg) and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in

vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-2,3,5,6-tetrahydro-4H-pyran-4-yl)-4-(4-fluorophenoxy)benzylamine (5.15 g) as an orange oil.

IR (Film) : 2927, 2845, 1498, 1464 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.7 (4H, m), 3.3-4.0 (4H, m), 3.80 (2H, s), 6.8-7.1 (6H, m), 7.2-7.4 (2H, m)

APCI-MASS (m/z) : 302 ($M+H^+$)

Preparation 145

The mixture of 4-(4-fluorophenoxy)benzaldehyde (3.24 g) and phenethylamine (2.73 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (60 ml). To this solution was added carefully sodium borohydride (567 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-(2-phenethyl)-4-(4-fluorophenoxy)benzylamine (4.73 g) as a yellow oil.

IR (Film) : 3061, 3028, 2927, 2821, 1608, 1497, 1454 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47 (1H, br s), 2.75-3.0 (4H, m), 3.77 (2H, s), 6.85-7.1 (6H, m), 7.15-7.35 (7H, m)

APCI-MASS (m/z) : 322 ($M+H^+$)

Preparation 146

The mixture of 4-(4-fluorophenoxy)benzaldehyde (4.32 g) and 2-ethoxyethylamine (3.57 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (80 ml). To this

solution was added carefully sodium borohydride (757 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-(2-ethoxyethyl)-4-(4-fluorophenoxy)benzylamine (5.50 g) as a yellow oil.

IR (Film) : 3053, 2976, 2929, 2866, 1608, 1498, 1456 cm^{-1}

NMR ($CDCl_3$, δ) : 1.20 (3H, t, J=7.0Hz), 2.8-2.9 (2H, m), 3.45-3.6 (4H, m), 3.78 (2H, s), 6.9-7.1 (6H, m), 7.25-7.35 (2H, m)

APCI-MASS (m/z) : 290 ($M+H^+$)

Preparation 147

The mixture of 3-(pyrazol-3-yl)benzaldehyde (1.27 g) and benzylamine (1.19 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (280 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-benzyl-3-(pyrazol-3-yl)benzylamine (1.22 g) as an oil.

IR (Film) : 3169, 3062, 3026, 2916, 2839, 1606, 1589, 1537, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 3.70 (2H, s), 3.7 (2H, s), 6.69 (1H, d, J=2.1Hz), 7.2-7.5 (7H, m), 7.7-7.9 (3H, s)

APCI-MASS (m/z) : 264 ($M+H^+$)

Preparation 148

The mixture of 3-(pyrazol-3-yl)benzaldehyde (1.72 g) and cyclohexylamine (1.49 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (30 ml). To this solution was added carefully sodium borohydride (378 mg) and the mixture was stirred at room temperature for 3 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cyclohexyl-3-(pyrazol-3-yl)benzylamine (1.15 g).

IR (KBr) : 3246, 3118, 3041, 2924, 2854, 1608, 1558 cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-2.0 (10H, m), 2.4-2.6 (1H, m), 3.88 (2H, s), 6.70 (1H, br s), 7.25-7.45 (2H, m), 7.6-7.9 (3H, m), 12.90 (1H, br s)

APCI-MASS (m/z) : 256 ($M+H^+$)

Preparation 149

The mixture of 3-(pyrazol-3-yl)benzaldehyde (1.72 g) and cyclopentylamine (1.70 g) was stirred at 120°C for 4 hours under nitrogen. The mixture was cooled to room temperature and dissolved in ethanol (40 ml). To this solution was added carefully sodium borohydride (378 mg), and the mixture was stirred at room temperature for 3 hours. The mixture was evaporated in vacuo and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give N-cyclopentyl-3-(pyrazol-3-yl)benzylamine (1.26 g).

IR (Film) : 3265, 1610, 1589 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (8H, m), 3.05-3.25 (1H,

m), 3.78 (2H, s), 6.68 (1H, s), 7.2-7.4 (2H, m), 7.6-7.9 (3H, m), 12.88 (1H, br)

APCI-MASS (m/z) : 242 ($M+H^+$)

Preparation 150

A mixture of 3-(1-tritylpyrazol-3-yl)benzaldehyde (1.72 g) and 4-fluorobenzylamine (0.57 ml) was stirred at 120°C for 4 hours. The mixture was cooled to room temperature and dissolved in ethanol (26 ml). To the mixture was added sodium borohydride (158 mg) and the reaction mixture was stirred at 50°C for 2 hours. The mixture was poured into water, extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (50:1)) to give N-(4-fluorobenzyl)-3-(1-tritylpyrazol-3-yl)benzylamine (1.40 g).

IR (Neat) : 3059, 2827, 1603, 1506, 1446, 1219 cm^{-1}

NMR ($CDCl_3$, δ) : 3.79 (2H, s), 3.82 (2H, s), 6.58 (1H, d, J=2.5Hz), 6.90-7.05 (2H, m), 7.10-7.45 (20H, m), 7.65-7.83 (2H, m)

FAB-MASS (m/z) : 524 ($M+H^+$)

Preparation 151

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.0 g) and 4-methoxybenzylamine (0.91 ml) was heated for 3 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (20 ml). To the solution was added sodium borohydride (220 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol

(10:1)) to give N-(4-methoxybenzyl)-3-(pyrazol-3-yl)benzylamine (1.17 g).

IR (Film) : 2370-3680 (br), 1610, 1512, 1248, 1036 cm^{-1}

NMR ($CDCl_3$, δ) : 3.77 (2H, s), 3.79 (3H, s), 3.84 (2H, s), 6.60 (1H, d, J=2.2Hz), 6.80-6.92 (2H, m), 7.17-7.41 (4H, m), 7.54-7.66 (2H, m), 7.85 (1H, s)

APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 152

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.0 g) and 4-fluorobenzylamine (0.8 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (20 ml). To the solution was added sodium borohydride (220 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (10:1)) to give N-(4-fluorobenzyl)-3-(pyrazol-3-yl)benzylamine (1.28 g).

IR (Film) : 2370-3680 (br), 1605, 1508, 1220, 1095 cm^{-1}

NMR ($CDCl_3$, δ) : 3.79 (2H, s), 3.84 (2H, s), 6.61 (1H, d, J=2.3Hz), 6.90-7.10 (2H, m), 7.18-7.45 (4H, m), 7.52-7.70 (2H, m), 7.75 (1H, s)

APCI-MASS (m/z) : 282 ($M+H^+$)

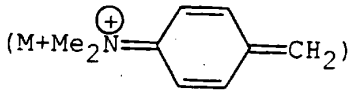
Preparation 153

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.2 g), 4-(dimethylamino)benzylamine·dihydrochloride (1.87 g) and triethylamine (11.7 ml) in toluene (30 ml) was refluxed for 5 hours. An insoluble material was removed by filtration

and evaporated in vacuo. The residue was dissolved in ethanol (18 ml). To the solution was added sodium borohydride (264 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (8:1)) to give N-[4-(dimethylamino)benzyl]-3-(pyrazol-3-yl)benzylamine (1.68 g).

IR (Film) : 2330-3700 (br), 1614, 1524, 1446, 1350, 804, 766 cm^{-1}

NMR ($CDCl_3$, δ) : 2.93 (6H, s), 3.75 (2H, s), 3.84 (2H, s), 6.59 (1H, d, J=2.2Hz), 6.65-6.75 (2H, m), 7.15-7.40 (4H, m), 7.55-7.66 (2H, m), 7.76 (1H, s)

APCI-MASS (m/z) : 440 

Preparation 154

The following compounds were obtained according to a similar manner to that of Preparation 57, 58, 59, 60, 62, 75, 76, 138, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153.

(1) N-Cycloheptyl-4-(4-chlorophenoxy)benzylamine

IR (Film) : 3035, 2925, 2855, 1610, 1590, 1505, 1485 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m), 3.76 (2H, s), 6.9-7.05 (4H, m), 7.25-7.4 (4H, m)

APCI-MASS (m/z) : 332, 330 ($M+H^+$)

(2) N-Cycloheptyl-4-(3-fluorophenoxy)benzylamine

IR (Neat) : 2926, 2854, 1599, 1483, 1269, 1213 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.10 (12H, m), 2.62-2.80 (1H, m), 3.77 (2H, s), 6.62-6.85 (3H, m), 6.93-7.05 (2H, m), 7.18-7.40 (3H, m)

APCI-MASS (m/z) : 314 ($M+H^+$)

(3) N-Cycloheptyl-4-(4-trifluoromethylphenoxy)benzylamine

IR (Neat) : 2926, 2854, 1601, 1504, 1462, 1327 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.00 (12H, m), 2.65-2.80 (1H, m), 3.78 (2H, s), 6.95-7.10 (4H, m), 7.30-7.40 (2H, m), 7.50-7.62 (2H, m)

APCI-MASS (m/z) : 364 ($M+H^+$)

(4) N-Cycloheptyl-4-(3,4-methylenedioxyphenoxy)benzylamine

IR (Neat) : 2924, 2854, 1606, 1502, 1481, 1354 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.95 (12H, m), 2.60-2.75 (1H, m), 3.74 (2H, s), 5.97 (2H, s), 6.47 (1H, dd, J=8.4, 2.4Hz), 6.56 (1H, d, J=2.4Hz), 6.75 (1H, d, J=8.4Hz), 6.85-6.96 (2H, m), 7.20-7.31 (2H, m)

APCI-MASS (m/z) : 340 ($M+H^+$)

(5) N-Cycloheptyl-4-(3,5-di-tert-butyl-4-methoxymethoxyphenoxy)benzylamine

IR (Film) : 2920, 2860, 1587 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 and 1.42 (total 18H, s), 1.4-2.2 (14H, m), 2.8-2.95 (1H, m), 3.62 and 3.64 (total 3H, s), 4.87 and 4.92 (total 2H, s), 6.92 (2H, s), 6.85-6.95 (2H, m), 7.4-7.5 (2H, m)

APCI-MASS (m/z) : 468 ($M+H^+$)

(6) N-Cycloheptyl-3-(4-fluorophenoxy)benzylamine

IR (Film) : 3062, 2926, 2854, 1608, 1583, 1502, 1446 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.6-2.8 (1H, m), 3.75 (2H, s), 6.8-7.3 (8H, m)

APCI-MASS (m/z) : 314 ($M+H^+$)

(7) N-Cycloheptyl-3-(1-tritylpyrazol-4-yl)benzylamine
NMR (DMSO-d_6, δ) : 1.2-1.9 (12H, m), 2.6-2.7 (1H, m), 3.70 (2H, s), 7.1-7.6 (19H, m), 7.76 (1H, s), 8.06 (1H, s)
APCI-MASS (m/z) : 512 ($M+H^+$)

(8) N-Cycloheptyl-3-(1-methylpyrazol-4-yl)benzylamine
IR (Neat) : 2926, 2852, 1610, 1460, 1410, 1230 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.63-2.80 (1H, m), 3.79 (2H, s), 3.94 (3H, s), 7.13-7.48 (4H, m), 7.63 (1H, s), 7.76 (1H, s)
APCI-MASS (m/z) : 284 ($M+H^+$)

(9) N-Cycloheptyl-3-(1-methylpyrazol-3-yl)benzylamine
IR (Neat) : 3400 (br), 2924, 2854, 1610, 1462, 1354, 1242 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-2.00 (12H, m), 2.64-2.80 (1H, m), 3.83 (2H, s), 3.95 (3H, s), 6.56 (1H, d, J=2.2Hz), 7.25-7.40 (3H, m), 7.60-7.78 (2H, m)
APCI-MASS (m/z) : 284 ($M+H^+$)

(10) N-Cycloheptyl-3-(1-methylpyrazol-5-yl)benzylamine
IR (Neat) : 2924, 2854, 1608, 1462, 1385, 1275 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.62-2.80 (1H, m), 3.83 (2H, s), 3.90 (3H, s), 6.31 (1H, d, J=1.8Hz), 7.25-7.48 (4H, m), 7.51 (1H, d, J=1.8Hz)
APCI-MASS (m/z) : 284 ($M+H^+$)

(11) N-Cycloheptyl-3-(imidazol-4-yl)benzylamine
IR (Film) : 2300-3600 (br), 2924, 2854, 1610, 1460 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-1.95 (12H, m), 2.55-2.75 (1H,

m), 3.73 (2H, s), 7.05-7.80 (6H, m), 12.00-12.25 (1H, br)

APCI-MASS (m/z) : 270 ($M+H^+$)

(12) N-Cycloheptyl-4-(5-methyl-1,3,4-oxadiazol-3-yl)benzylamine

IR (KBr) : 3442, 3292, 3211, 2920, 2852, 1689, 1576, 1502, 1450 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.40 (12H, m), 2.61 (3H, s), 2.63-2.80 (1H, m), 3.87 (2H, s), 7.45-7.54 (2H, m), 7.93-8.05 (2H, m)

APCI-MASS (m/z) : 286 ($M+H^+$)

(13) N-Cycloheptyl-4-(4-benzyl-5-methyl-4H-1,2,4-triazol-3-yl)benzylamine

IR (Neat) : 3298, 2924, 2852, 1612, 1527, 1458, 1358 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.93 (12H, m), 2.38 (3H, s), 2.60-2.77 (1H, m), 3.81 (2H, s), 5.16 (2H, s), 6.90-7.05 (2H, m), 7.27-7.55 (7H, m)

APCI-MASS (m/z) : 375 ($M+H^+$)

(14) N-Cycloheptyl-3-(2-methyl-2H-tetrazol-5-yl)benzylamine

IR (Neat) : 2924, 2854, 1520, 1462, 1365 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.65-2.80 (1H, m), 3.86 (2H, s), 4.40 (3H, s), 7.40-7.48 (2H, m), 7.95-8.05 (1H, m), 8.09 (1H, s)

APCI-MASS (m/z) : 286 ($M+H^+$)

(15) N-Cycloheptyl-3-(1-methyl-1H-tetrazol-5-yl)benzylamine

IR (Neat) : 2924, 2854, 1533, 1452, 1292 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.65-2.80 (1H, m), 3.88 (2H, s), 4.18 (3H, s), 7.46-7.65 (3H, m), 7.75 (1H, s)

APCI-MASS (m/z) : 286 ($M+H^+$)

(16) N-Cycloheptyl-4-(1H-1,2,4-triazol-1-yl)benzylamine
mp : 53-54°C
IR (KBr) : 3101, 2922, 2852, 1518, 1460, 1277, 1147, 984 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-2.00 (12H, m), 2.60-2.80 (1H, m), 3.84 (2H, s), 7.40-7.55 (2H, m), 7.55-7.70 (2H, m), 8.10 (1H, s), 8.54 (1H, s)
APCI-MASS (m/z) : 271 ($M+H^+$)

(17) N-Cycloheptyl-4-(1H-1,2,3-triazol-1-yl)benzylamine
mp : 78-79°C
IR (KBr) : 3319, 3124, 2920, 2852, 1520, 1230, 1101, 1041 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-2.00 (12H, m), 2.63-2.80 (1H, m), 3.87 (2H, s), 7.45-7.57 (2H, m), 7.64-7.76 (2H, m), 7.85 (1H, s), 7.98 (1H, s)
APCI-MASS (m/z) : 271 ($M+H^+$)

(18) N-Cycloheptyl-4-(2H-1,2,3-triazol-2-yl)benzylamine
IR (Neat) : 2926, 2854, 1608, 1514, 1460, 1412, 1381, 1259, 951, 824 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-1.90 (12H, m), 2.50-2.70 (1H, m), 3.74 (2H, s), 7.45-7.55 (2H, m), 7.90-8.00 (2H, m), 8.10 (2H, s)
APCI-MASS (m/z) : 271 ($M+H^+$)

(19) N-Cycloheptyl-(4-methylpiperazin-1-yl)benzylamine
IR (Film) : 2925, 2850, 2795, 1615, 1515 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.21 (3H, s), 2.4-2.5 (4H, m), 3.1-3.2 (4H, m), 3.2-3.45 (1H, m), 6.85 (2H, d, J=8.5Hz), 7.15 (2H, d, J=8.5Hz)
APCI-MASS (m/z) : 302 ($M+H^+$)

(20) N-Cycloheptyl-4-(4-methylsulfonylaminophenyl)-benzylamine

IR (KBr) : 3020, 2930, 2855, 1605, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-2.0 (12H, m), 2.5-2.7 (1H, m), 3.01 (3H, s), 3.72 (2H, s), 7.27 (2H, d, J=8.5Hz), 7.39 (2H, d, J=8.5Hz), 7.57 (2H, d, J=8.2Hz), 7.63 (2H, d, J=8.2Hz)

APCI-MASS (m/z) : 373($M+H^+$)

(21) N-Cycloheptyl-4-(N-benzoylsulfamoyl)benzylamine

IR (KBr) : 3477, 3057, 2927, 2858, 1599, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-2.2 (12H, m), 3.1-3.3 (1H, m), 4.17 (2H, s), 7.2-7.45 (5H, m), 7.4-7.5 (2H, m), 7.75-7.9 (2H, m), 8.4-8.7 (1H, br)

APCI-MASS (m/z) : 387 ($M+H^+$)

(22) N-Cycloheptyl-4-(N-phenylsulfonylcarbamoyl)benzylamine

IR (KBr) : 3091, 2929, 2858, 1647, 1601, 1537 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-2.2 (12H, m), 3.1-3.3 (1H, m), 4.11 (2H, s), 7.35-7.5 (5H, m), 7.8-7.9 (2H, m), 7.93 (2H, d, J=8.1Hz)

APCI-MASS (m/z) : 387 ($M+H^+$)

(23) N-Cycloheptyl-4-(3-pyridylmethyl)benzylamine

IR (Film) : 3304, 3026, 2924, 2852, 1574, 1512 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.2 (12H, m), 2.6-2.8 (1H, m), 3.75 (2H, s), 3.95 (2H, s), 7.1-7.5 (6H, m), 8.45 (1H, dd, J=4.8, 1.8Hz), 8.49 (1H, d, J=1.8Hz)

APCI-MASS (m/z) : 295 ($M+H^+$)

(24) N-Cycloheptyl-4-(4-pyridylmethyl)benzylamine

IR (Film) : 3323, 3022, 2924, 2852, 1599 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.1 (12H, m), 2.6-2.8 (1H, m), 3.77 (2H, s), 3.94 (2H, s), 7.09 (1H, dd, J=4.5, 1.6Hz), 7.12 (2H, d, J=9.4Hz), 7.29 (1H, d, J=9.4Hz), 8.48 (2H, dd, J=4.5, 1.6Hz)

APCI-MASS (m/z) : 295 ($M+H^+$)

(25) N-Cycloheptyl-4-(pyrazol-1-ylmethyl)benzylamine
IR (Neat) : 2924, 2854, 1514, 1458, 1090, 750 cm^{-1}
NMR ($CDCl_3$, δ) : 1.30-1.98 (12H, m), 2.56-2.77 (1H, m), 3.76 (2H, s), 5.30 (2H, s), 6.27 (1H, dd, J=2.0Hz), 7.10-7.40 (5H, m), 7.54 (1H, d, J=2.0Hz)
APCI-MASS (m/z) : 284 ($M+H^+$)

(26) N-Cycloheptyl-4-(imidazol-1-ylmethyl)benzylamine
IR (Neat) : 3280 (br), 2924, 2854, 1506, 1458, 1230, 1107, 1076 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.95 (12H, m), 2.60-2.78 (1H, m), 3.76 (2H, s), 5.10 (2H, s), 6.90 (1H, s), 7.00-7.40 (5H, m), 7.54 (1H, s)
APCI-MASS (m/z) : 284 ($M+H^+$)

(27) N-Cycloheptyl-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methylamine
NMR (DMSO-d_6, δ) : 1.17 (3H, s), 1.3-1.9 (4H, m), 1.97 (3H, s), 2.01 (3H, s), 2.04 (3H, s), 2.5-2.7 (3H, m), 7.39 (1H, s)
APCI-MASS (m/z) : 332 ($M+H^+$)

(28) N-Cycloheptyl-4-[N-(3,5-di-tert-butyl-4-hydroxyphenyl)carbamoyl]benzylamine
IR (KBr) : 3639, 3304, 2926, 2858, 1643, 1606, 1547 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 1.39 (18H, s), 2.5-2.7 (1H, m), 3.77 (2H, s), 6.78 (1H, s), 7.45 (2H, d, J=8.2Hz), 7.88 (2H, d, J=8.2Hz), 7.58 (2H, s), 9.87 (1H, s)
APCI-MASS (m/z) : 451 ($M+H^+$)

(29) N-Cycloheptyl-4-[N-(4-fluorophenyl)carbamoyl]-benzylamine
IR (KBr) : 3354, 2927, 2854, 1651, 1612, 1529,

1512 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.5-2.65 (1H, m), 3.77 (2H, s), 7.1-7.3 (2H, m), 7.75-7.85 (2H, m), 7.47 (2H, d, J=8.2Hz), 7.89 (2H, d, J=8.2Hz), 10.22 (1H, s)

APCI-MASS (m/z) : 341 ($M+H^+$)

(30) N-Cycloheptyl-4-[N-(4-fluorophenyl)-N-methylcarbamoyl]benzylamine

IR (KBr) : 3475, 3187, 3120, 3024, 2927, 2853, 1643, 1597, 1541, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.4-2.6 (1H, m), 3.33 (3H, s), 3.60 (2H, s), 7.05-7.3 (8H, m)

APCI-MASS (m/z) : 355 ($M+H^+$)

(31) N-Cycloheptyl-4-(tert-butyldimethylsilyloxymethyl)-benzylamine

IR (Film) : 2927, 2850, 1514, 1464 cm^{-1}

NMR (DMSO-d_6, δ) : 0.08 (6H, s), 0.89 (9H, s), 1.3-1.9 (12H, m), 2.5-2.65 (1H, m), 3.67 (2H, s), 4.67 (2H, s), 7.22 (2H, d, J=8.3Hz), 7.28 (2H, d, J=8.3Hz)

APCI-MASS (m/z) : 348 ($M+H^+$)

(32) N-Benzyl-3-phenoxybenzylamine

IR (Film) : 3062, 3030, 2829, 1583, 1487, 1452 cm^{-1}

NMR (DMSO-d_6, δ) : 2.63 (1H, br s), 3.64 (2H, s), 3.66 (2H, s), 6.8-7.45 (14H, m)

APCI-MASS (m/z) : 290 ($M+H^+$)

(33) N-Benzyl-3-(4-fluorophenoxy)benzylamine

IR (Film) : 3062, 3030, 2916, 2829, 1608, 1584, 1500, 1450 cm^{-1}

NMR ($CDCl_3$, δ) : 3.78 (2H, s), 3.79 (2H, s), 6.8-7.4 (13H, m)

APCI-MASS (m/z) : 308 ($M+H^+$)

(34) N-Benzyl-3-(1-Methylpyrazol-3-yl)benzylamine
IR (Neat) : 3313, 3028, 2935, 1608, 1498, 1452, 1356, 1242 cm^{-1}
NMR ($CDCl_3$, δ) : 3.83 (2H, s), 3.85 (2H, s), 3.95 (3H, s), 6.55 (1H, d, J=2.3Hz), 7.18-7.42 (8H, m), 7.64-7.73 (1H, m), 7.77(1H, s)
APCI-MASS (m/z) : 278 ($M+H^+$)

(35) N-Benzyl-3-(1-methylpyrazol-5-yl)benzylamine
IR (Neat) : 3310, 3026, 2830, 1606, 1454, 1387, 1275 cm^{-1}
NMR ($CDCl_3$, δ) : 3.84 (2H, s), 3.87 (2H, s), 3.89 (3H, s), 6.31 (1H, d, J=1.9Hz), 7.20-7.45 (9H, m), 7.51 (1H, d, J=1.9Hz)
APCI-MASS (m/z) : 278 ($M+H^+$)

(36) N-Benzyl-4-(1-methylpyrazol-3-yl)benzylamine
IR (Neat) : 3310, 3028, 2937, 2820, 1504, 1454, 1430 cm^{-1}
NMR ($CDCl_3$, δ) : 3.81 (2H, s), 3.83 (2H, s), 3.95 (3H, s), 6.53 (1H, d, J=2.3Hz), 7.18-7.43 (8H, m), 7.70-7.80 (2H, m)
APCI-MASS (m/z) : 278 ($M+H^+$)

(37) N-Benzyl-4-(1-methylpyrazol-5-yl)benzylamine
IR (Neat) : 3305, 3026, 2820, 1493, 1454, 1385, 1275 cm^{-1}
NMR ($CDCl_3$, δ) : 3.85 (2H, s), 3.87 (2H, s), 3.89 (3H, s), 6.30 (1H, d, J=1.9Hz), 7.20-7.50 (9H, m), 7.51 (1H, d, J=1.9Hz)
APCI-MASS (m/z) : 278 ($M+H^+$)

(38) N-Benzyl-4-(pyrazol-3-yl)benzylamine

IR (Neat) : 2250-3680 (br), 1514, 1495, 1454, 1350 cm^{-1}

NMR (DMSO-d_6, δ) : 3.69 (4H, s), 6.67 (1H, d, J=2.1Hz), 7.15-7.50 (7H, m), 7.60-7.90 (3H, m), 12.81, 13.20 (total 1H, each br)

APCI-MASS (m/z) : 264 ($M+H^+$)

(39) N-Benzyl-4-(1-methylpyrazol-4-yl)benzylamine

mp : 90-91°C

IR (KBr) : 3300, 3020, 2914, 2854, 1570, 1473, 1452, 1194, 1097 cm^{-1}

NMR ($CDCl_3$, δ) : 3.81 (2H, s), 3.82 (2H, s), 3.94 (3H, s), 7.20-7.50 (9H, m), 7.60 (1H, s), 7.75 (1H, s)

APCI-MASS (m/z) : 278 ($M+H^+$)

(40) N-Benzyl-3-(imidazol-4-yl)benzylamine

IR (Neat) : 2200-3560 (br), 1608, 1491, 1454 cm^{-1}

NMR (DMSO-d_6, δ) : 3.72 (4H, s), 7.10-7.40 (7H, m), 7.41-7.80 (4H, m)

APCI-MASS (m/z) : 264 ($M+H^+$)

(41) N-Benzyl-3-(2-methyl-2H-tetrazol-5-yl)benzylamine

IR (Neat) : 3028, 2825, 1520, 1452, 1363, 804 cm^{-1}

NMR ($CDCl_3$, δ) : 3.84 (2H, s), 3.89 (2H, s), 4.40 (3H, s), 7.20-7.52 (7H, m), 7.96-8.07 (1H, m), 8.12 (1H, s)

APCI-MASS (m/z) : 280 ($M+H^+$)

(42) N-Benzyl-3-(1-methylpyrazol-4-yl)benzylamine

IR (Neat) : 3305, 3028, 2935, 2827, 1610, 1450, 1363, 1230 cm^{-1}

NMR ($CDCl_3$, δ) : 3.84 (4H, s), 3.94 (3H, s), 7.13-7.40 (8H, m), 7.45 (1H, s), 7.62 (1H, s), 7.77 (1H, s)

APCI-MASS (m/z) : 278 ($M+H^+$)

(43) N-(4-Methoxybenzyl)-4-(4-fluorophenoxy)benzylamine
IR (Neat) : 3001, 2903, 2833, 1610, 1500, 1460, 1248, 1210 cm^{-1}
NMR ($CDCl_3$, δ) : 3.75 (2H, s), 3.76 (2H, s), 3.80 (3H, s), 6.82-7.10 (8H, m), 7.20-7.35 (4H, m)
APCI-MASS (m/z) : 338 ($M+H^+$)

Preparation 155

The following compound was obtained according to a similar manner to that of Preparation 31, 38, 39 or 89.

4-(1-Tritylpyrazol-4-yl)toluene
NMR (DMSO-d_6, δ) : 2.27 (3H, s), 7.1-7.5 (19H, m), 7.73 (1H, s), 8.04 (1H, s)

Preparation 156

The following compounds were obtained according to a similar manner to that of Preparation 28.

(1) 4-(1-Tritylpyrazol-4-yl)benzyl bromide
NMR (DMSO-d_6, δ) : 4.70 and 4.77 (total 2H, s), 7.0-7.8 (21H, m)

(2) 3-Benzoylbenzyl bromide
IR (Film) : 3059, 3028, 1686, 1599 cm^{-1}
NMR ($CDCl_3$, δ) : 4.53 (2H, s), 7.35-7.9 (9H, m)
APCI-MASS (m/z) : 277, 275 ($M+H^+$)

Preparation 157

The following compounds were obtained according to a similar manner to that of Preparation 63.

(1) N-Cycloheptyl-4-(1-tritylpyrazol-4-yl)benzylamine
IR (Film) : 3057, 3028, 2918, 2852, 1641, 1605, 1566 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-2.0 (12H, m), 2.55-2.75 (1H, m), 3.68 and 3.75 (total 2H, s), 7.05-7.25 (5H, m), 7.3-8.1 (16H, m)
APCI-MASS (m/z) : 512 ($M+H^+$)

(2) N-Cycloheptyl-4-(2-cyanophenyl)benzylamine
IR (Film) : 3060, 3030, 2910, 2855, 2225, 1597, 1480 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.65-2.85 (1H, m), 3.85 (2H, s), 7.4-7.8 (8H, m)
APCI-MASS (m/z) : 305 ($M+H^+$)

(3) N-Cycloheptyl-4-[2-(1-trityl-1H-tetrazol-5-yl)phenyl]benzylamine
IR (KBr) : 3058, 3026, 2924, 2854, 1603, 1493, 1446 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.6-2.75 (1H, m), 3.68 (2H, s), 6.8-6.95 (5H, m), 7.01 (2H, d, J=7.9Hz), 7.20 (2H, d, J=7.9Hz), 7.3-7.8 (14H, m)
FAB-MASS (m/z) : 590 ($M+H^+$)

(4) N-Cycloheptyl-3-benzoylbenzylamine
IR (Film) : 3059, 2927, 2855, 1653, 1599, 1580 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.85 (2H, s), 7.3-7.8 (9H, m)
APCI-MASS (m/z) : 308 ($M+H^+$)

Preparation 158

The following compounds were obtained according to a similar manner to that of Preparation 50 or 51.

(1) 3-(1-Methylpyrazol-3-yl)benzaldehyde
IR (Neat) : 2941, 2829, 2730, 1695, 1606, 1585, 1439, 1242 cm^{-1}
NMR ($CDCl_3$, δ) : 3.98 (3H, s), 6.62 (1H, d, J=2.2Hz),

7.42 (1H, d, J=2.2Hz), 7.51-7.62 (1H, m), 7.77-7.86 (1H, m), 8.05-8.13 (1H, m), 8.25-8.32 (1H, m), 10.07 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

(2) 3-(1-Methylpyrazol-5-yl)benzaldehyde

mp : 72-74°C

IR (KBr) : 3041, 2831, 2733, 1697, 1579, 1462, 1377 cm^{-1}

NMR ($CDCl_3$, δ) : 3.94 (3H, s), 6.39 (1H, d, J=1.4Hz), 7.56 (1H, d, J=1.4Hz), 7.58-7.74 (2H, m), 7.89-7.97 (2H, m), 10.09 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

(3) 4-(Pyrazol-1-yl)benzaldehyde

mp : 53-55°C

IR (KBr) : 3109, 2833, 2744, 1693, 1608, 1394, 1213, 760 cm^{-1}

NMR ($CDCl_3$, δ) : 5.43 (2H, s), 6.34 (1H, dd, J=2.1, 2.1Hz), 7.25-7.35 (2H, m), 7.45 (1H, d, J=2.1Hz), 7.59 (1H, d, J=2.1Hz), 7.80-7.90 (2H, m), 9.99 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

(4) 4-(Imidazol-1-ylmethyl)benzaldehyde

IR (Neat) : 2600-3600 (br), 1695, 1506, 1232, 1076, 818, 737 cm^{-1}

NMR ($CDCl_3$, δ) : 5.22 (2H, s), 6.85-7.95 (7H, m), 10.01 (1H, s)

APCI-MASS (m/z) : 187 ($M+H^+$)

Preparation 159

The following compound was obtained according to a similar manner to that of Preparation 47.

3-(Imidazol-4-yl)benzaldehyde

mp : 135-138°C

IR (KBr) : 2080-3390 (br), 1691, 1606, 1479, 1327, 1186, 1066, 978, 781 cm^{-1}

NMR (DMSO-d_6, δ) : 7.59 (1H, dd, J=7.6, 7.6Hz), 7.67-7.80 (3H, m), 8.05-8.15 (1H, m), 8.31 (1H, s), 10.04 (1H, s), 12.30 (1H, br)

APCI-MASS (m/z) : 173 ($M+H^+$)

Preparation 160

The following compounds were obtained according to a similar manner to that of Preparation 44, 45, 84, 110, 124 or 126.

(1) 4-(5-Methyl-1,3,4-oxadiazol-2-yl)benzaldehyde

IR (KBr) : 2829, 1701, 1610, 1590, 1550, 1421 cm^{-1}

NMR ($CDCl_3$, δ) : 2.66 (3H, s), 7.96-8.07 (2H, m), 8.15-8.26 (2H, m), 10.10 (1H, s)

APCI-MASS (m/z) : 189 ($M+H^+$)

(2) 4-(4-Benzyl-5-methyl-4H-1,2,4-triazol-3-yl)benzaldehyde

IR (KBr) : 3450 (br), 1689, 1608, 1572, 1531, 1207 cm^{-1}

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 5.22 (2H, s), 6.93-7.07 (2H, m), 7.30-7.47 (3H, m), 7.70-7.80 (2H, m), 7.90-8.00 (2H, m), 10.05 (1H, s)

APCI-MASS (m/z) : 278 ($M+H^+$)

Preparation 161

The following compound was obtained according to a similar manner tc that of Preparation 97.

4-Benzyl-2-(4-hydroxymethyl)phenyl-5-methyl-4H-1,2,4-triazole

mp : 118-121°C

IR (KBr) : 2600-3650 (br), 1535, 1487, 1425, 1363, 1039, 854, 739 cm^{-1}

NMR ($CDCl_3$, δ) : 2.36 (3H, s), 3.10-3.25 (1H, m), 4.65-4.77 (2H, m), 5.14 (2H, s), 6.90-7.03 (2H, m), 7.25-7.50 (7H, m)

APCI-MASS (m/z) : 280 ($M+H^+$)

Preparation 162

The following compound was obtained according to a similar manner to that of Preparation 31.

N-Methyl-N-methoxy-4-[4-(methylsulfonylamino)phenyl]-benzamide

IR (KBr) : 3210, 2935, 1630, 1608, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 3.04 (3H, s), 3.28 (3H, s), 3.58 (3H, s), 7.32 (2H, d, J=8.6Hz), 7.6-7.8 (6H, m), 9.91 (1H, s)

Preparation 163

The following compounds were obtained according to a similar manner to that of Preparation 36.

(1) 4-(4-Methylsulfonylaminophenyl)benzaldehyde

IR (KBr) : 3290, 2995, 2840, 2745, 1695, 1600, 1525, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 3.06 (3H, s), 7.33 (2H, d, J=8.5Hz), 7.78 (2H, d, J=8.5Hz), 7.89 (2H, d, J=8.2Hz), 7.98 (2H, d, J=8.2Hz), 9.98 (1H, br s), 10.04 (1H, s)

APCI-MASS (m/z) : 276 ($M+H^+$)

(2) 4-(N-Benzoylsulfamoyl)benzaldehyde

IR (KBr) : 3381, 3057, 2883, 1697, 1599, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 7.3-7.5 (3H, m), 7.9-8.0 (2H, m), 7.44 (2H, d, J=8.3Hz), 8.00 (2H, d, J=8.3Hz),

10.03 (1H, s)
APCI-MASS (m/z) : 290 ($M+H^+$)

Preparation 164

The following compounds were obtained according to a similar manner to that of Preparation 33 or 34.

(1) 4-(N-Methyl-N-methoxysulfamoyl)benzamide
IR (KBr) : 3292, 3201, 3111, 2979, 2943, 1605, 1562, 1504 cm^{-1}
NMR (DMSO-d_6, δ) : 3.28 (3H, s), 3.54 (3H, s), 7.49 (2H, br s), 7.74 (2H, d, J=8.4Hz), 7.88 (2H, d, J=8.4Hz)
APCI-MASS (m/z) : 245 ($M+H^+$)

(2) N-Methyl-N-methoxy-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide
IR (KBr) : 3479, 2983, 2935, 2870, 1655 cm^{-1}
NMR (DMSO-d_6, δ) : 1.49 (3H, s), 1.97 (3H, s), 2.05 (6H, s), 1.6-1.75 (1H, m), 2.4-2.6 (3H, m), 3.34 (3H, s), 3.57 (3H, s), 7.48 (1H, s)
APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 165

The following compound was obtained according to a similar manner to that of Preparation 105.

4-(N-Phenylsulfonylcarbamoyl)benzaldehyde
IR (KBr) : 3185, 3155, 3105, 2935, 2850, 1740, 1695, 1645, 1605, 1565, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 6.95 (2H, d, J=7.5Hz), 7.35-7.45 (2H, m), 7.75-7.9 (3H, m), 8.20 (2H, d, J=7.5Hz), 10.02 (1H, s)
APCI-MASS (m/z) : 290 ($M+H^+$)

Preparation 166

The following compound was obtained according to a similar manner to that of Preparation 66.

N-Cycloheptyl-3-benzylbenzylamine

IR (Film) : 3059, 3026, 2926, 2852, 1601, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.0 (12H, m), 2.6-2.8 (1H, m), 3.74 (2H, s), 3.97 (2H, s), 7.0-7.5 (9H, m)

APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 167

The following compound was obtained according to a similar manner to that of Preparation 36.

2-Formyl-6-hydroxy-2,5,7,8-tetramethylchromane

IR (KBr) : 3541, 2981, 2933, 2872, 2833, 2727, 1732 cm^{-1}

NMR (DMSO-d_6, δ) : 1.66 (3H, s), 1.7-1.9 (1H, m), 2.2-2.65 (3H, m), 1.97 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 7.55 (1H, s), 9.53 (1H, s)

APCI-MASS (m/z) : 244 ($M+H^+$)

Preparation 168

To a solution of 2-chloro-6-methyl-4-methylthio-3-nitropyridine (13.25 g) in methanol (150 ml) was added 28% sodium methoxide in methanol (23.4 ml), and the mixture was refluxed for 7 hours under nitrogen. The mixture was cooled and the precipitates were collected by filtration, washed with methanol and diisopropyl ether and dried under phosphorus pentoxide to give 2-methoxy-6-methyl-4-methylthio-3-nitropyridine (10.29 g) as a yellow powder.

IR (KBr) : 3024, 2997, 2951, 2924, 2856, 1587, 1541, 1495, 1452 cm^{-1}

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 2.57 (3H, s), 3.94 (3H, s), 7.07 (1H, s)

APCI-MASS (m/z) : 215 ($M+H^+$)

Preparation 169

To a solution of 2,4-dichloro-6-methyl-3-nitropyridine (41.40 g) in methanol (400 ml) was added dropwise a 28% solution of sodium methoxide in methanol (38.6 ml), and the mixture was stirred at 60°C for an hour under nitrogen. The mixture was evaporated in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 2-chloro-4-methoxy-6-methyl-3-nitropyridine (30.43 g) as a pale yellow crystal.

IR (KBr) : 3088, 2987, 2953, 2883, 1601, 1552, 1524, 1471 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 4.01 (3H, s), 7.42 (1H, s)

Preparation 170

To a solution of 2-chloro-4-methoxy-6-methyl-3-nitropyridine (30.42 g) in methanol (300 ml) was added dropwise a solution of sodium methanethiolate (12.63 g) in methanol (200 ml) at room temperature and the mixture was stirred at 50°C for 4 hours under nitrogen. The mixture was evaporated in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-methoxy-2-methylthio-6-methyl-3-nitropyridine (30.23 g) as a yellow powder.

IR (KBr) : 3066, 2997, 2956, 2933, 2858, 1585, 1549, 1514, 1466 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 2.53 (3H, s), 3.95 (3H, s), 7.11 (1H, s)

APCI-MASS (m/z) : 215 ($M+H^+$)

Preparation 171

To a suspension of 4-methoxy-2-methylthio-6-methyl-3-nitropyridine (30.15 g) in ethanol (300 ml) was added conc. hydrochloric acid (58.6 ml), and the mixture was refluxed for 10 hours. The mixture was cooled to 5°C and the precipitates were collected by filtration, washed with ethanol and diisopropyl ether, and dried in vacuo under phosphorus pentoxide to give 4-hydroxy-2-methylthio-6-methyl-3-nitropyridine (19.79 g) as a yellow powder.

IR (KBr) : 2989, 2920, 2783, 1551, 1518 cm^{-1}

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 2.50 (3H, s), 6.62 (1H, s)

Preparation 172

To a suspension of 4-hydroxy-2-methylthio-6-methyl-3-nitropyridine (30.65 g) in phosphorus oxychloride (140.8 g) was stirred at 100°C for 10 hours. The mixture was poured into a mixture of ethyl acetate and water, and neutralized by addition of 5N sodium hydroxide aqueous solution. The insoluble materials were filtered off, and the filtrate was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 4-chloro-2-methylthio-6-methyl-3-nitropyridine (11.87 g) as a yellow powder.

IR (KBr) : 3103, 3053, 2933, 1560, 1518 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55 (3H, s), 2.59 (3H, s), 7.55 (1H, s)

APCI-MASS (m/z) : 221, 219 ($M+H^+$)

Preparation 173

To a solution of 2,4-dichloro-6-methyl-3-nitropyridine (4.14 g) in 1,4-dioxane (50 ml) and methanol (50 ml) was added Raney Nickel (NDT-90, purchased from Kawaken Fine Chemicals) (ca. 2 g), and the mixture was hydrogenated for

4 hours under atmospheric pressure. Raney Nickel was filtered off and washed with methanol, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-amino-2,4-dichloro-6-methylpyridine (3.53 g) as a yellow oil.

IR (Film) : 3479, 3385, 3221, 3188, 2924, 1616, 1576, 1543, 1471 cm^{-1}

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 5.52 (2H, br s), 7.23 (1H, s)

APCI-MASS (m/z) : 181, 179, 177 ($M+H^+$)

Preparation 174

To a solution of 3-amino-2,4-dichloro-6-methylpyridine (3.51 g) in dichloromethane (50 ml) was added N,N-dimethylaniline (2.88 g) at 5°C, followed by dropwise addition of phenyl chloroformate (3.41 g), and the mixture was stirred at room temperature for 3.5 hours. The mixture was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from diisopropyl ether and the crystal was collected by filtration, washed with diisopropyl ether and dried in vacuo to give 2,4-dichloro-6-methyl-3-phenoxycarbonylaminopyridine (1.96 g).

IR (KBr) : 3282, 3244, 3184, 3013, 1718, 1637, 1608, 1524, 1491 cm^{-1}

NMR (DMSO-d_6, δ) : 2.27 (3H, s), 7.1-7.5 (5H, m), 7.65 (1H, s), 10.10 (1H, br s)

APCI-MASS (m/z) : 301, 299, 297 ($M+H^+$)

Preparation 175

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.0 g) and 2-methoxybenzylamine (0.91 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (20 ml). To the solution was added sodium borohydride (220 mg) and stirred for two hours at

ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (10:1)) to give N-(2-methoxybenzyl)-3-(pyrazol-3-yl)benzylamine (1.06 g).

IR (Film) : 2400-3600 (br), 1603, 1493, 1462, 1244 cm^{-1}

NMR ($CDCl_3$, δ) : 3.81 (3H, s), 3.84 (2H, s), 3.85 (2H, s), 6.59 (1H, d, J=2.2Hz), 6.80-6.98 (2H, m), 7.17-7.50 (4H, m), 7.53-7.67 (2H, m), 7.79 (1H, s)

APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 176

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.0 g) and 3-methoxybenzylamine (0.91 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (20 ml). To the solution was added sodium borohydride (220 mg), and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (15:1)) to give N-(3-methoxybenzyl)-3-(pyrazol-3-yl)benzylamine (1.24 g).

IR (Neat) : 2370-3680 (br), 1603, 1487, 1439, 1263, 1157, 1045 cm^{-1}

NMR ($CDCl_3$, δ) : 3.80 (3H, s), 3.81 (2H, s), 3.85 (2H, s), 6.61 (1H, d, J=2.2Hz), 6.75-6.85 (1H, m), 6.86-6.97 (2H, m), 7.19-7.43 (3H, m), 7.55-7.68 (2H, m), 7.76 (1H, s)

APCI-MASS (m/z) : 294 ($M+H^+$)

Preparation 177

A mixture of 4-(4-fluorophenoxy)benzaldehyde (1.5 g) and 3-phenylpropylamine (1.19 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (30 ml). To the solution was added sodium borohydride (262 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (15:1)) to give N-(3-phenylpropyl)-4-(4-fluorophenoxy)-benzylamine (1.92 g).

IR (Neat) : 3028, 2929, 2856, 2818, 1606, 1497, 1454, 1250, 1211 cm^{-1}

NMR ($CDCl_3$, δ) : 1.85 (2H, qn, J=7.4Hz), 2.55-2.75 (4H, m), 3.75 (2H, s), 6.83-7.10 (6H, m), 7.10-7.36 (7H, m)

APCI-MASS (m/z) : 336 ($M+H^+$)

Preparation 178

A mixture of 3-(pyrazol-3-yl)benzaldehyde (1.0 g) and phenethylamine (0.875 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (20 ml). To the solution was added sodium borohydride (220 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with dichloromethane - methanol (15:1 to 10:1)) to give N-(2-phenylethyl)-3-(pyrazol-3-yl)benzylamine (1.27 g).

IR (Neat) : 2300-3700 (br), 1606, 1495, 1452, 1354, 1097 cm^{-1}

NMR ($CDCl_3$, δ) : 2.76-3.00 (4H, m), 3.86 (2H, s), 6.59 (1H, d, J=2.2Hz), 7.10-7.43 (7H, m), 7.53-7.68 (2H, m), 7.86 (1H, s)

APCI-MASS (m/z) : 278 ($M+H^+$)

Preparation 179

A mixture of 4-(4-fluorophenoxy)benzaldehyde (1.5 g) and (S)-1-phenylethylamine (1.08 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (30 ml). To the solution was added sodium borohydride (262 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with n-hexane - ethyl acetate (4:1 to 2:1) to give N-[(S)-1-phenylethyl]-4-(4-fluorophenoxy)benzylamine (2.23 g).

IR (Neat) : 3028, 2966, 2831, 1606, 1498, 1452, 1250, 1213 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38 (3H, d, J=6.6Hz), 3.56 (1H, d, J=13.1Hz), 3.63 (1H, d, J=13.1Hz), 3.82 (1H, q, J=6.6Hz), 6.83-7.12 (6H, m), 7.15-7.43 (7H, m)

APCI-MASS (m/z) : 322 ($M+H^+$)

$[\alpha]_D^{29}$: -31.2° (C=1.05, $CHCl_3$)

Preparation 180

A mixture of 4-(4-fluorophenoxy)benzaldehyde (1.5 g) and (R)-1-phenylethylamine (1.08 ml) was heated for 4 hours at 120°C. After cooling to room temperature, the mixture was dissolved in ethanol (30 ml). To the solution was added sodium borohydride (262 mg) and stirred for two hours at ambient temperature. The reaction mixture was poured into water and extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate. The solvent

was removed in vacuo and the residue was chromatographed on silica gel (50 g, eluting with n-hexane - ethyl acetate (4:1 to 2:1) to give N-[(R)-1-phenylethyl]-4-(4-fluorophenoxy)benzylamine (2.12 g).

IR (Neat) : 3028, 2966, 2831, 1606, 1498, 1452, 1250, 1213 cm^{-1}

NMR ($CDCl_3$, δ) : 1.37 (3H, d, J=6.6Hz), 3.56 (1H,d, J=13.1Hz), 3.63 (1H, d, J=13.1Hz), 3.81 (1H, q, J=6.6Hz), 6.83-7.12 (6H, m), 7.15-7.42 (7H, m)

APCI-MASS (m/z) : 322 ($M+H^+$)

$[\alpha]_D^{30}$: +31.7° (C=1.02, $CHCl_3$)

Preparation 181

The following compounds were obtained according to a similar manner to that of Preparation 71, 78 or 173.

(1) 3-Amino-2-methoxy-6-methyl-6-methylthiopyridine

IR (Film) : 3444, 3352, 2984, 2947, 2922, 2860, 1585, 1559, 1462 cm^{-1}

NMR (DMSO-d_6, δ) : 2.26 (3H, s), 2.43 (3H, s), 3.84 (3H, s), 4.39 (2H, br s), 6.64 (1H, s)

APCI-MASS (m/z) : 185 ($M+H^+$)

(2) 3-Amino-4-chloro-2-methylthio-6-methylpyridine

IR (KBr) : 3417, 3300, 3207, 2922, 1618, 1558 cm^{-1}

NMR (DMSO-d_6, δ) : 2.31 (3H, s), 2.51 (3H, s), 4.96 (2H, br s), 6.96 (1H, s)

APCI-MASS (m/z) : 191, 189 ($M+H^+$)

Preparation 182

The following compounds were obtained according to a similar manner to that of Preparation 74 or 79.

(1) 2-Methoxy-6-methyl-4-methylthio-3-phenoxycarbonylaminopyridine

IR (KBr) : 3217, 1740, 1700, 1649, 1541, 1518 cm^{-1}

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 2.45 (3H, s), 3.86 (3H, s), 6.81 (1H, s), 7.0-7.5 (5H, m), 8.76 and 9.17 (total 1H, br s)

APCI-MASS (m/z) : 305 ($M+H^+$)

(2) 4-Chloro-2-methylthio-6-methyl-3-phenoxycarbonyliminopyridine

IR (KBr) : 3207, 3026, 3001, 2926, 1724, 1597, 1554, 1524, 1489 cm^{-1}

NMR (DMSO-d_6, δ) : 2.48 (3H, s), 2.51 (3H, s), 7.0-7.5 (6H, m), 9.37 and 9.77 (total 1H, br s)

APCI-MASS (m/z) : 311, 309 ($M+H^+$)

Preparation 183

The following compound was obtained according to a similar manner to that of Example 7, 8, 9, 10, 13, 14, 15, 16 or 17.

1-[4-(4-Fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3305, 3107, 2924, 1633, 1574, 1498 cm^{-1}

NMR (DMSO-d_6, δ) : 2.39 (6H, s), 2.44 (3H, s), 4.22 (2H, d, J=5.8Hz), 6.53-6.7 (1H, br), 6.86 (1H, s), 6.9-7.4 (8H, m), 7.54 (1H, br s)

APCI-MASS (m/z) : 444 ($M+H^+$)

Example 1

To a solution of N-(4-biphenylylmethyl)-cycloheptylamine (559 mg) in dichloromethane (10 ml) was added 2,4,6-trimethylphenylisocyanate (322 mg), and the mixture was stirred at room temperature for 1.3 hours under nitrogen. The mixture was evaporated in vacuo and the crystalline compound was collected by filtration using hexane:ethyl acetate (5:1) to give 1-(4-biphenylylmethyl)-1-cycloheptyl-3-(2,4,6-trimethylphenyl)urea (710 mg).

IR (KBr) : 3320, 2920, 2855, 1625, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (12H, m), 2.00 (6H, s), 2.20 (3H, s), 4.4-4.55 (1H, m), 4.55 (2H, s), 5.48 (1H, s), 6.79 (2H, s), 7.3-7.65 (9H, m)

APCI-MASS (m/z) : 441 ($M+H^+$)

Example 2

To a solution of N-(4-biphenylylmethyl)-cycloheptylamine (559 mg) in dichloromethane (10 ml) was added 2,6-diisopropylphenylisocyanate (406 mg), and the mixture was stirred at room temperature for 1.1 hours. The mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 1-(4-biphenylylmethyl)-1-cycloheptyl-3-(2,6-diisopropylphenyl)urea (885 mg) as a crystal.

IR (KBr) : 3415, 3340, 3060, 3030, 2960, 2930, 2865, 1625, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 0.9-1.3 (10H, m), 1.5-1.8 (12H, m), 1.95-2.1 (2H, m), 2.8-3.0 (2H, m), 4.4-4.6 (1H, m), 4.56 (2H, s), 5.47 (1H, s), 7.0-7.65 (12H, m)

APCI-MASS (m/z) : 483 ($M+H^+$)

Example 3

To a solution of 2-amino-4,6-dimethoxypyrimidine (465 mg) and triphosgene (297 mg) in 1,2-dichloroethane (20 ml)

was added triethylamine (304 mg) and the mixture was refluxed for 1.8 hours. The mixture was cooled to room temperature and a solution of N-(4-biphenylylmethyl)-cycloheptylamine (559 mg) in 1,2-dichloroethane (10 ml) was added thereto. After being stirred at room temperature for 3.1 hours, the mixture was poured into water and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-(4-biphenylylmethyl)-1-cycloheptyl-3-(4,6-dimethoxypyrimidin-2-yl)urea (205 mg).

IR (KBr) : 3390, 3225, 2925, 2855, 1685, 1600, 1525 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 3.86 (6H, s), 4.25-4.45 (1H, m), 4.58 (2H, s), 6.88 (1H, s), 7.3-7.6 (9H, m)

APCI-MASS (m/z) : 461 ($M+H^+$)

Example 4

To a solution of 2,4,6-trifluoroaniline (441 mg) and triphosgene (297 mg) in dichloromethane (10 ml) was added triethylamine (304 mg) at 5°C and the mixture was refluxed for 2 hours under nitrogen. The mixture was cooled to room temperature and a solution of N-(4-biphenylylmethyl)-cycloheptylamine (559 mg) in dichloromethane (3 ml) was added. The mixture was stirred at room temperature for 1.2 hours and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-(4-biphenylylmethyl)-1-cycloheptyl-3-(2,4,6-trimethylphenyl)urea (752 mg).

IR (KBr) : 3285, 2930, 2860, 1635, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45-2.15 (12H, m), 4.3-4.45 (1H, m), 4.59 (2H, s), 5.58 (1H, s), 6.55-6.7 (2H, m), 7.3-7.65 (9H, m)

APCI-MASS (m/z) : 453 ($M+H^+$)

Example 5

The following compounds were obtained according to similar manners to those of Examples 1, 2, 3 and 4.

(1) 1-Cycloheptyl-1-(4-phenoxyphenylmethyl)-3-(2,6-diisopropylphenyl)urea
IR (KBr) : 3415, 3360, 2960, 2925, 2865, 1645, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : 0.9-1.35 (12H, m), 1.4-2.1 (12H, m), 2.8-3.0 (2H, m), 4.35-4.5 (1H, m), 4.50 (2H, s), 5.46 (1H, s), 6.95-7.45 (12H, m)
APCI-MASS (m/z) : 499 ($M+H^+$)

(2) 1-(3-Biphenylylmethyl)-1-cycloheptyl-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3325, 2925, 2855, 1625, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 1.97 (6H, s), 2.20 (3H, s), 4.2-4.4 (1H, m), 4.57 (2H, s), 5.49 (1H, s), 6.78 (2H, s), 7.3-7.7 (9H, m)
APCI-MASS (m/z) : 441 ($M+H^+$)

(3) 1-(2-Biphenylylmethyl)-1-cycloheptyl-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3285, 2970, 2930, 2860, 1635, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 1.96 (6H, s), 2.21 (3H, s), 4.25-4.4 (1H, m), 4.37 (2H, s), 5.30 (1H, s), 6.80 (2H, s), 7.2-7.7 (9H, m)
APCI-MASS (m/z) : 441 ($M+H^+$)

(4) 1-Cycloheptyl-1-(4-phenoxyphenylmethyl)-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3295, 2920, 2855, 1620, 1590, 1510, 1490 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.8 (12H, m), 2.00 (6H, s), 2.22 (3H, s), 4.35-4.5 (1H, m), 4.48 (2H, s),

5.47 (1H, s), 6.81 (2H, s), 7.0-7.4 (9H, m)
APCI-MASS (m/z) : 457 ($M+H^+$)

(5) 1-Cycloheptyl-1-(3-phenoxyphenylmethyl)-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3310, 2925, 2855, 1625, 1605, 1585, 1510 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.8 (12H, m), 2.00 (6H, s), 2.21 (3H, s), 4.25-4.45 (1H, m), 4.47 (2H, s), 5.44 (1H, s), 6.80 (2H, s), 6.85-7.4 (9H, m)
APCI-MASS (m/z) : 457 ($M+H^+$)

(6) 1-Cycloheptyl-1-[4-(pyridin-2-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3410, 3320, 2920, 2855, 1625, 1585, 1560, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.8 (12H, m), 2.03 (6H, s), 2.20 (3H, s), 4.3-4.5 (1H, m), 4.58 (2H, s), 5.49 (1H, s), 6.80 (2H, s), 7.2-7.3 (1H, m), 7.51 (2H, d, J=8.3Hz), 7.7-7.85 (2H, m), 8.02 (2H, d, J=8.3Hz), 8.7-8.75 (1H, m)
APCI-MASS (m/z) : 442 ($M+H^+$)

(7) 1-Cycloheptyl-1-[4-(pyridin-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3315, 2920, 2855, 1645, 1510 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.9 (12H, m), 2.02 (6H, s), 2.21 (3H, s), 4.35-4.5 (1H,m), 4.58 (2H, s), 5.48 (1H, s), 6.80 (2H, s), 7.39 (1H, dd, J=7.9, 4.9Hz), 7.3-7.7 (4H, m), 7.86 (1H, dt, J=8.2, 1.8Hz), 8.60 (1H, d, J=3.6Hz), 8.83 (1H, s)
APCI-MASS (m/z) : 442 ($M+H^+$)

(8) 1-Cycloheptyl-1-[[2-(4-chlorophenyl)thiazol-4-

yl]methyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3300, 2920, 2855, 1645, 1610, 1495 cm^{-1}
NMR ($CDCl_3$, δ) : 1.5-2.0 (12H, m), 2.13 (6H, s), 2.24 (3H, s), 4.2-4.4 (1H, m), 4.61 (2H, s), 6.85 (2H, s), 7.18 (1H, s), 7.24 (1H, s), 7.35-7.45 (2H, m), 7.8-7.9 (2H, m)
APCI-MASS (m/z) : 483 ($M+H^+$)

(9) 1-Cycloheptyl-1-[(2-phenylimidazol-5-yl)methyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3100, 2925, 2855, 1620, 1570 cm^{-1}
NMR (DMSO-d_6, δ) : 1.35-1.8 (12H, m), 2.06 (6H, s), 2.21 (3H, s), 4.05-4.2 (1H, m), 4.36 (2H, s), 6.83 (2H, s), 7.23 (1H, s), 7.3-7.5 (3H, m), 7.8-7.9 (2H, m), 8.68 (1H, s), 12.55 (1H, s)
APCI-MASS (m/z) : 431 ($M+H^+$)

(10) 1-Cycloheptyl-1-[4-(pyrrol-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3310, 2920, 2855, 1625, 1525, 1510 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 2.01 (6H, s), 2.21 (3H, s), 4.3-4.5 (1H, m), 4.53 (2H, s), 5.46 (1H, s), 6.3-6.4 (2H, m), 6.80 (2H, s), 7.05-7.15 (2H, m), 7.35-7.5 (4H, m)
APCI-MASS (m/z) : 430 ($M+H^+$)

(11) 1-Cycloheptyl-1-[3-(pyrrol-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3320, 2920, 2855, 1625, 1610, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.45-2.05 (12H, m), 2.01 (6H, s), 2.21 (3H, s), 4.3-4.5 (1H, m), 4.56 (2H, s), 5.47 (1H, s), 6.35-6.4 (2H, m), 6.80 (2H, s), 7.05-7.10 (2H, m), 7.25-7.5 (4H, m)
APCI-MASS (m/z) : 430 ($M+H^+$)

(12) 1-Cycloheptyl-1-[[4-(pyrrol-1-yl)pyridin-2-yl]methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3220, 2920, 1645, 1605, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.8 (12H, m), 2.13 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.56 (2H, s), 6.35-6.4 (2H, m), 6.84 (2H, s), 6.5-6.55 (2H, m), 6.55-6.65 (2H, m), 8.50 (1H, br s), 8.51 (1H, d, J=5.6Hz)

APCI-MASS (m/z) : 431 ($M+H^+$)

(13) 1-Cycloheptyl-1-[(6-phenylpyridin-3-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3315, 2920, 2855, 1630, 1560, 1515 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 2.09 (6H, s), 2.23 (3H, s), 4.1-4.3 (1H, m), 4.60 (2H, s), 5.53 (1H, s), 6.83 (2H, s), 7.35-7.55 (3H, m), 7.7-7.9 (2H, m), 7.95-8.05 (2H, m), 8.70 (1H, s)

APCI-MASS (m/z) : 442 ($M+H^+$)

(14) 1-Cycloheptyl-1-[3-(2-methylthiazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3360, 2925, 2855, 1620, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 1.98 (6H, s), 2.20 (3H, s), 2.78 (3H, s), 4.4-4.55 (1H, m), 4.57 (2H, s), 5.49 (1H, s), 6.78 (2H, s), 7.33 (1H, s), 7.35-7.5 (2H, m), 7.79 (1H, d, J=7.1Hz), 7.93 (1H, s)

APCI-MASS (m/z) : 462 ($M+H^+$)

(15) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3405, 3210, 2925, 2855, 1640, 1610, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.9 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.1-4.25 (1H, m), 4.54 (2H, s),

6.63 (1H, s), 6.82 (2H, s), 7.2-7.8 (6H, m), 12.86 (1H, s)

APCI-MASS (m/z) : 431 ($M+H^+$)

(16) 1-Benzyl-1-(4-phenoxybenzyl)-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3310, 3030, 2915, 1630, 1590, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 2.01 (6H, s), 2.22 (3H, s), 4.63 (2H, s), 5.64 (1H, s), 6.82 (2H, s), 7.0-7.4 (14H, m)

APCI-MASS (m/z) : 451 ($M+H^+$)

(17) 1-Furfuryl-1-(4-phenoxybenzyl)-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3280, 3030, 2975, 2915, 1625, 1595, 1530, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 2.10 (6H, s), 2.25 (3H, s), 4.55 (2H, s), 4.61 (2H, s), 6.03 (1H, s), 6.25-6.3 (1H, m), 6.35-6.4 (1H, m), 6.86 (2H, s), 6.95-7.45 (10H, m)

APCI-MASS (m/z) : 441 ($M+H^+$)

(18) 1-Cycloheptyl-1-[4-(4-chlorophenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3300, 2925, 2855, 1655, 1625, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.05 (12H, m), 2.01 (6H, s), 2.21 (3H, s), 4.3-4.5 (1H, m), 4.55 (2H, s), 5.46 (1H, s), 6.80 (2H, s), 7.4-7.65 (8H, m)

APCI-MASS (m/z) : 476 ($M+H^+$)

(19) 1-Cycloheptyl-1-[4-(4-fluorophenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3300, 2925, 2855, 1655, 1625, 1490 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.15 (12H, m), 2.01 (6H, s), 2.21 (3H, s), 4.4-4.6 (1H, m), 4.55 (2H, s), 5.47 (1H, s), 6.80 (2H, s), 7.05-7.2 (2H, m), 7.45-7.6 (6H, m)

APCI-MASS (m/z) : 459 ($M+H^+$)

(20) 1-Cycloheptyl-1-[4-(4-bromophenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3300, 2920, 2855, 1655, 1625, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.05 (12H, m), 2.01 (6H, s), 2.21 (3H, s), 4.35-4.55 (2H, s), 5.46 (1H, s), 6.80 (2H, s), 7.45-7.6 (8H, m)

APCI-MASS (m/z) : 521 ($M+H^+$)

(21) 1-Cycloheptyl-1-[4-(4-methylphenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3310, 3020, 2920, 2855, 1660, 1625, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 1.99 (6H, s), 2.20 (3H, s), 2.40 (3H, s), 4.35-4.55 (1H, m), 4.54 (2H, s), 5.48 (1H, s), 6.79 (2H, s), 7.25 (2H, d, J=7.9Hz), 7.4-7.5 (4H, m), 7.59 (2H, d, J=8.3Hz)

APCI-MASS (m/z) : 455 ($M+H^+$)

(22) 1-Cycloheptyl-1-[4-(4-dimethylaminophenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3405, 3325, 2920, 2855, 2805, 1650, 1610, 1535, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.2 (12H, m), 1.98 (6H, s), 2.20 (3H, s), 3.00 (6H, s), 4.4-4.6 (1H, m), 4.52 (2H, s), 5.50 (1H, s), 7.4-7.65 (8H, m)

APCI-MASS (m/z) : 484 ($M+H^+$)

(23) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3410, 3325, 2920, 2855, 1635, 1585, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.01 (6H, s), 2.22 (3H, s), 4.35-4.55 (1H, m), 4.49 (2H, s), 5.46 (1H, s), 6.81 (2H, s), 6.85-7.05 (4H, m), 7.3-7.5 (4H, m)
APCI-MASS (m/z) : 537 ($M+H^+$)

(24) 1-Cycloheptyl-1-(4-benzoylbenzyl)-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3325, 2920, 2855, 1655, 1605, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 2.06 (6H, s), 2.22 (3H, s), 4.2-4.4 (1H, m), 4.61 (2H, s), 5.45 (1H, s), 6.82 (2H, s), 7.5-7.7 (5H, m), 7.75-7.9 (4H, m)
APCI-MASS (m/z) : 469 ($M+H^+$)

(25) 1-Cycloheptyl-1-(4-benzylbenzyl)-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3305, 3025, 2920, 2855, 1625, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.5-2.05 (12H, m), 1.93 (6H, s), 2.21 (3H, s), 3.97 (2H, s), 4.35-4.55 (1H, m), 4.46 (2H, s), 5.42 (1H, s), 6.78 (2H, s), 7.1-7.4 (9H, m)
APCI-MASS (m/z) : 455 ($M+H^+$)

(26) 1-Cycloheptyl-1-(4-phenylthiobenzyl)-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3315, 2920, 1630, 1610, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 2.00 (6H, s), 2.22 (3H, s), 4.3-4.5 (1H, m), 4.48 (2H, s), 5.42 (1H, s), 6.81 (2H, s), 7.07 (1H, t, J=8.6Hz), 7.25-7.45 (8H, m)

APCI-MASS (m/z) : 473 ($M+H^+$)

(27) 1-Cycloheptyl-1-[(6-phenylthiopyridin-3-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3310, 2925, 2855, 1630, 1585, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.05 (12H, m), 2.05 (6H, s), 2.23 (3H, s), 4.05-4.2 (1H, m), 4.47 (2H, s), 5.49 (1H, s), 6.84 (2H, s), 6.90 (1H, d, J=8.3Hz), 7.4-7.65 (6H, m), 8.43 (1H, d, J=1.8Hz)

APCI-MASS (m/z) : 474 ($M+H^+$)

(28) 1-Cycloheptyl-1-(4-benzoylaminobenzyl)-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3350, 3055, 2920, 2855, 1655, 1610, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.06 (6H, s), 2.19 (3H, s), 4.1-4.3 (1H, m), 4.51 (2H, s), 6.81 (2H, s), 7.05 (1H, d, J=7.7Hz), 7.29 (1H, d, J=7.7Hz), 7.40 (1H, s), 7.5-7.7 (4H, m), 7.77 (1H, s), 7.9-8.0 (2H, m), 10.26 (1H, s)

APCI-MASS (m/z) : 484 ($M+H^+$)

(29) 1-Cycloheptyl-1-[4-(phenylcarbamoyl)benzyl)-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3425, 3300, 2920, 2860, 1670, 1635, 1600, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.11 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.58 (2H, s), 6.85 (2H, s), 7.13 (1H, t, J=7.3Hz), 7.3-7.5 (4H, m), 7.65 (1H, s), 7.77 (2H, d, J=7.6Hz), 7.93 (2H, d, J=8.2Hz), 10.17 (1H, s)

APCI-MASS (m/z) : 484 ($M+H^+$)

(30) 1-Cycloheptyl-1-[4-(2-pyridylcarbamoyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3335, 2920, 2855, 1675, 1635, 1610, 1580, 1525, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.10 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.57 (2H, s), 6.84 (2H, s), 7.16 (1H, dd, J=6.8, 5.8Hz), 7.42 (2H, d, J=8.2Hz), 7.63 (1H, br s), 7.8-7.9 (1H, m), 8.00 (2H, d, J=8.2Hz), 8.19 (1H, d, J=8.4Hz), 8.35-8.45 (1H, m), 10.71 (1H, s)

APCI-MASS (m/z) : 485 ($M+H^+$)

(31) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3305, 2920, 2855, 1630, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.00 (6H, s), 2.22 (3H, s), 4.3-4.5 (1H, m), 4.76 (2H, s), 5.47 (1H, s), 6.82 (2H, s), 6.9-7.1 (6H, m), 7.36 (2H, d, J=8.5Hz)

APCI-MASS (m/z) : 475 ($M+H^+$)

(32) 1-Cycloheptyl-1-[4-(phenylsulfamoyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3395, 3130, 2925, 2860, 1635, 1600, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.8 (12H, m), 2.01 (6H, s), 2.20 (3H, s), 4.05-4.25 (1H, m), 4.50 (2H, s), 6.81 (2H, s), 7.0-7.15 (3H, m), 7.15-7.3 (2H, m), 7.42 (2H, d, J=8.3Hz), 7.57 (1H, br s), 7.70 (2H, d, J=8.3Hz), 10.23 (1H, s)

APCI-MASS (m/z) : 520 ($M+H^+$)

(33) 1-Cycloheptyl-1-[4-(phenylsulfonylamino)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3410, 3110, 2925, 2860, 1630, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.8 (12H, m), 1.99 (6H, s), 2.20 (3H, s), 4.0-4.2 (1H, m), 4.37 (2H, s), 6.81

(2H, s), 7.01 (2H, d, J=8.3Hz), 7.15 (2H, d, J=8.3Hz), 7.37 (1H, br s), 7.5-7.65 (3H, m), 7.7-7.8 (2H, m), 10.22 (1H, br s)

APCI-MASS (m/z) : 520 ($M+H^+$)

(34) 1-Cycloheptyl-1-[4-(3-thienyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3320, 2920, 1624, 1504, 1252, 775 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.00 (6H, s), 2.20 (3H, s), 4.35-4.55 (1H, m), 4.53 (2H, s), 5.47 (1H, s), 6.79 (2H, s), 7.34-7.50 (5H, m), 7.55-7.66 (2H, m)

APCI-MASS (m/z) : 447 ($M+H^+$)

(35) 1-Cycloheptyl-1-[4-(2-thienyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3319, 2922, 1624, 1504, 1253, 849 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.01 (6H, s), 2.20 (3H, s), 4.35-4.55 (1H, m), 4.52 (2H, s), 5.46 (1H, s), 6.79 (2H, s), 7.09 (1H, dd, J=5.1, 3.6Hz), 7.25-7.35 (2H, m), 7.36-7.46 (2H, m), 7.58-7.68 (2H, m)

APCI-MASS (m/z) : 447 ($M+H^+$)

(36) 1-Cycloheptyl-1-[4-(pyrazol-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3325, 2922, 1628, 1504, 1394 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.08 (12H, m), 2.04 (6H, s), 2.21 (3H, s), 4.28-4.48 (1H, m), 4.55 (2H, s), 5.48 (1H, s), 6.48 (1H, t, J=2.3Hz), 6.81 (2H, s), 7.42-7.54 (2H, m), 7.65-7.78 (3H, m), 7.92 (1H, d, J=2.3Hz)

APCI-MASS (m/z) : 431 ($M+H^+$)

(37) 1-Cycloheptyl-1-[4-(imidazol-1-yl)benzyl]-3-(2,4,6-

trimethylphenyl)urea
IR (KBr) : 3310, 2922, 1637, 1520, 1305 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 2.05 (6H, s), 2.22 (3H, s), 4.20-4.40 (1H, m), 4.57 (2H, s), 5.47 (1H, s), 6.83 (2H, s), 7.21 (1H, s), 7.28 (1H, s), 7.33-7.44 (2H, m), 7.45-7.57 (2H, m), 7.85 (1H, s)
APCI-MASS (m/z) : 431 ($M+H^+$)

(38) 1-Cycloheptyl-1-[4-(1-methylpyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3321, 2922, 1628, 1504, 1209, 955 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.08 (12H, m), 1.99 (6H, s), 2.20 (3H, s), 3.95 (3H, s), 4.35-4.55 (1H, m), 4.50 (2H, s), 5.47 (1H, s), 6.79 (2H, s), 7.32-7.53 (4H, m), 7.61 (1H, s), 7.75 (1H, s)
APCI-MASS (m/z) : 445 ($M+H^+$)

(39) 1-Cycloheptyl-1-[(2-phenylthiophen-5-yl)methyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3329, 2922, 1624, 1510, 758 cm^{-1}
NMR ($CDCl_3$, δ) : 1.42-2.15 (12H, m), 2.04 (6H, s), 2.22 (3H, s), 4.25-4.43 (1H, m), 4.63 (2H, s), 5.82 (1H, s), 6.81 (2H, s), 7.02 (1H, d, J=3.6Hz), 7.16 (1H, d, J=3.6Hz), 7.22-7.43 (3H, m), 7.50-7.61 (2H, m)
APCI-MASS (m/z) : 447 ($M+H^+$)

(40) 1-Cycloheptyl-1-[4-(oxazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3302, 2922, 1624, 1508, 1105, 941 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.08 (12H, m), 2.03 (6H, s), 2.21 (3H, s), 4.30-4.50 (1H, m), 4.55 (2H, s), 5.45 (1H, s), 6.81 (2H, s), 7.36 (1H, s), 7.42-7.53 (2H, m), 7.63-7.74 (2H, m), 7.92 (1H, s)

APCI-MASS (m/z) : 432 ($M+H^+$)

(41) 1-Cycloheptyl-1-[(2-phenylfuran-5-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3340, 2920, 1628, 1508, 762 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.15 (12H, m), 2.09 (6H, s), 2.23 (3H, s), 4.22-4.41 (1H, m), 4.53 (2H, s), 5.93 (1H, s), 6.41 (1H, d, J=3.3Hz), 6.62 (1H, d, J=3.3Hz), 6.83 (2H, s), 7.20-7.43 (3H, m), 7.57-7.67 (2H, m)

APCI-MASS (m/z) : 431 ($M+H^+$)

(42) 1-Cycloheptyl-1-[(5-phenylisoxazol-3-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3326, 2924, 1630, 1512, 766 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.14 (6H, s), 2.24 (3H, s), 4.05-4.25 (1H, m), 4.56 (2H, s), 6.14 (1H, s), 6.63 (1H, s), 6.86 (2H, s), 7.40-7.53 (3H, m), 7.70-7.82 (2H, m)

APCI-MASS (m/z) : 432 ($M+H^+$)

(43) 1-Cycloheptyl-1-[(3-phenylpyrazol-5-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 2700-3600 (br), 2924, 1633, 1508, 1250, 1201 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 2.12 (6H, s), 2.23 (3H, s), 3.92-4.12 (1H, m), 4.47 (2H, s), 6.24 (1H, br s), 6.50 (1H, s), 6.84 (2H, s), 7.25-7.46 (3H, m), 7.62-7.75 (2H, m)

APCI-MASS (m/z) : 431 ($M+H^+$)

(44) 1-Cycloheptyl-1-[(4-phenylthiophen-2-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3315, 2922, 2854, 1628, 1508, 1377, 1308 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.13 (12H, m), 2.03 (6H, s), 2.21 (3H, s), 4.26-4.45 (1H, m), 4.66 (2H, s), 5.82 (1H, s), 6.81 (2H, s), 7.21-7.45 (5H, m), 7.50-7.60 (2H, m)

APCI-MASS (m/z) : 447 ($M+H^+$)

(45) 1-Cycloheptyl-1-[4-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 2800-3500 (br), 2924, 2856, 1645, 1504, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 2.00 (6H, s), 2.19 (3H, s), 4.35-4.55 (1H, m), 4.54 (2H, s), 5.51 (1H, s), 6.60 (1H, d, J=2.3Hz), 6.78 (2H, s), 7.42-7.53 (2H, m), 7.55 (1H, d, J=2.3Hz), 7.73-7.83 (2H, m)

APCI-MASS (m/z) : 431 ($M+H^+$)

(46) 1-Cycloheptyl-1-[4-(1-methylpyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3406, 3331, 2924, 2856, 1647, 1502, 1236, 849, 758 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.08 (12H, m), 2.00 (6H, s), 2.20 (3H, s), 3.96 (3H, s), 4.35-4.55 (1H, m), 4.52 (2H, s), 5.50 (1H, s), 6.54 (1H, d, J=2.3Hz), 6.78 (2H, s), 7.35-7.47 (3H, m), 7.77-7.87 (2H, m)

APCI-MASS (m/z) : 445 ($M+H^+$)

(47) 1-Cycloheptyl-1-[4-(1-methylpyrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3296, 2922, 2854, 1628, 1506, 1385 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 2.02 (6H, s), 2.21 (3H, s), 3.89 (3H, s), 4.32-4.50 (1H, m), 4.57 (2H, s), 5.45 (1H, s), 6.30 (1H, d, J=1.9Hz), 6.81 (2H, s), 7.39-7.56 (5H, m),

APCI-MASS (m/z) : 445 ($M+H^+$)

(48) 1-Cycloheptyl-1-[3-(1-trityl-1H-tetrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3340, 2924, 2856, 1649, 1495, 1448, 1240 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 1.96 (6H, s), 2.20 (3H, s), 4.30-4.50 (1H, m), 4.57 (2H, s), 5.42 (1H, s), 6.77 (2H, s), 7.08-7.57 (17H, m), 8.05-8.18 (2H, m)

(49) 1-Cycloheptyl-1-[4-phenoxybenzyl-3-(4,6-dimethoxypyrimidin-2-yl)]urea
IR (KBr) : 3390, 2925, 2860, 1685, 1595 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 3.87 (6H, s), 4.2-4.4 (1H, m), 4.51 (2H, s), 5.66 (1H, s), 6.87 (1H, s), 6.95-7.4 (9H, m)
APCI-MASS (m/z) : 477 ($M+H^+$)

(50) 1-Cycloheptyl-1-(4-phenylbenzyl)-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3360, 2925, 2855, 1660, 1565 cm^{-1}
NMR ($CDCl_3$, δ) : 1.45-2.1 (12H, m), 2.36 (3H, s), 2.45 (3H, s), 2.46 (3H, s), 4.3-4.5 (1H, m), 4.62 (2H, s), 5.52 (1H, s), 6.59 (1H, s), 7.3-7.7 (9H, m)
APCI-MASS (m/z) : 506 ($M+H^+$)

(51) 1-(3-Phenylbenzyl)-1-cycloheptyl-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3285, 2925, 2860, 1635, 1610, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 4.3-4.5 (1H, m), 4.62 (2H, s), 5.60 (1H, s), 6.55-6.7 (2H, m), 7.3-7.65 (9H, m)
APCI-MASS (m/z) : 453 ($M+H^+$)

(52) 1-(2-Phenylbenzyl)-1-cycloheptyl-3-(2,4,6-

trifluorophenyl)urea
IR (KBr) : 3415, 3320, 3060, 3020, 2920, 2855, 1625, 1575 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 4.2-4.35 (1H, m), 4.40 (2H, s), 5.50 (1H, s), 6.55-6.75 (2H, m), 7.25-7.6 (9H, m)
APCI-MASS (m/z) : 453 ($M+H^+$)

(53) 1-Cycloheptyl-1-(4-phenoxybenzyl)-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3285, 2925, 2860, 1635, 1590, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 4.2-4.4 (1H, m), 4.51 (2H, s), 5.58 (1H, s), 6.6-6.75 (2H, m), 7.0-7.4 (9H, m)
APCI-MASS (m/z) : 469 ($M+H^+$)

(54) 1-Cycloheptyl-1-(3-phenoxybenzyl)-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3280, 2930, 2860, 1635, 1615, 1585, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 4.2-4.4 (1H, m), 4.50 (2H, s), 5.55 (1H, s), 6.6-6.75 (2H, m), 6.9-7.4 (9H, m)
APCI-MASS (m/z) : 469 ($M+H^+$)

(55) 1-Cycloheptyl-1-[4-(pyridin-2-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3285, 2925, 2860, 1635, 1610, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 4.25-4.4 (1H, m), 4.61 (2H, s), 5.59 (1H, s), 6.6-6.75 (2H, m), 7.2-7.3 (1H, m), 7.47 (2H, d, J=8.4Hz), 7.7-7.8 (2H, m), 8.02 (2H, d, J=8.4Hz), 8.65-8.75 (1H, m)
APCI-MASS (m/z) : 454 ($M+H^+$)

(56) 1-Benzyl-1-[[2-(4-chlorophenyl)thiazol-4-yl]methyl]-3-

(2,4,6-trifluorophenyl)urea
IR (KBr) : 3270, 3090, 1665, 1640, 1615, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 4.54 (2H, s), 4.64 (2H, s), 6.65-6.8 (2H, m), 7.3-7.4 (5H, m), 7.34 (1H, s), 7.4-7.5 (2H, m), 7.85-7.95 (2H, m)
APCI-MASS (m/z) : 488 ($M+H^+$)

(57) 1-(Cycloheptyl-1-[4-(pyrrol-1-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3285, 2925, 2860, 1635, 1610, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.05 (12H, m), 4.2-4.4 (1H, m), 4.56 (2H, s), 5.57 (1H, s), 6.3-6.4 (2H, m), 6.55-6.7 (2H, m), 7.05-7.15 (2H, m), 7.41 (4H, s)
APCI-MASS (m/z) : 442 ($M+H^+$)

(58) 1-Cycloheptyl-1-[4-(3-thienyl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3300, 2927, 1637, 1518, 1120, 777 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40-2.08 (12H, m), 4.27-4.47 (1H, m), 4.56 (2H, s), 5.58 (1H, s), 6.58-6.73 (2H, m), 7.30-7.50 (5H, m), 7.57-7.70 (2H, m)
APCI-MASS (m/z) : 459 ($M+H^+$)

(59) 1-Cycloheptyl-1-[4-(2-thienyl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3300, 2930, 1635, 1520, 1120 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.08 (12H, m), 4.25-4.45 (1H, m), 4.55 (2H, s), 5.57 (1H, s), 6.55-6.72 (2H, m), 7.09 (1H, dd, J=5.1, 3.6Hz), 7.22-7.42 (4H, m), 7.57-7.70 (2H, m)
APCI-MASS (m/z) : 459 ($M+H^+$)

Example 6

To a stirred suspension of 1-cycloheptyl-1-[3-(1-trityl-1H-tetrazol-5-yl)benzyl]-3-(2,4,6-

trimethylphenyl)urea (1.46 g) in methanol (14 ml) was added conc. hydrochloric acid (0.722 ml). The mixture was stirred for one hour at room temperature. Insoluble white solid was collected by filtration, washed with methanol (x2), water (x3) to give 1-cycloheptyl-1-[3-(1H-tetrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea (0.79 g).

IR (KBr) : 3359, 2400-3300 (br), 1595, 1512, 1456, 1257 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-1.90 (12H, m), 2.06 (6H, s), 2.20 (3H, s), 4.14-4.34 (1H, m), 4.59 (2H, s), 6.82 (2H, s), 7.46-7.66 (2H, m), 7.80-7.90 (1H, m), 8.00-8.08 (1H, m)

APCI-MASS (m/z) : 433 ($M+H^+$)

Example 7

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)benzylamine (2.51 g) in toluene (100 ml) were added 3-phenoxycarbonylamino-2,4-bis(methylthio)-6-methylpyridine (2.56 g) and triethylamine (2.43 g) and the mixture was refluxed for 4 hours under nitrogen. The mixture was cooled and poured into a mixture of ethyl acetate and water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (3.89 g).

IR (KBr) : 3379, 3080, 3055, 2924, 2856, 1651, 1568, 1529, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-2.0 (12H, m), 2.39 (6H, s), 2.44 (3H, s), 4.0-4.2 (1H, m), 4.45 (2H, s), 6.86 (1H, s), 6.93 (2H, d, J=8.5Hz), 7.0-7.1 (2H, m), 7.15-7.3 (2H, m), 7.36 (2H, d, J=8.5Hz), 7.83 (1H, br s)

APCI-MASS (m/z) : 540 ($M+H^+$)

Example 8

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)benzylamine (1.57 g) in toluene (150 ml) were added 2,4-dimethoxy-6-methyl-3-phenoxycarbonylaminopyridine (1.44 g) and triethylamine (1.52 g), and the mixture was refluxed for 3 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4-dimethoxy-6-methylpyridin-3-yl)urea (1.83 g).

IR (KBr) : 3388, 3062, 2927, 2856, 1668, 1599, 1498 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.35 (3H, s), 3.67 and 3.77 (6H, s x 2), 4.0-4.2 (1H, m), 4.43 (2H, s), 6.63 (1H, s), 6.95-7.4 (8H, m)

APCI-MASS (m/z) : 496 ($M+H^+$)

Example 9

To a suspension of N-benzyl-3-(pyrazol-3-yl)benzylamine bis(trifluoroacetate) (2.46 g) in toluene (80 ml) were added 2,4-bis(methylthio)-6-methyl-3-phenoxycarbonylaminopyridine (1.60 g) and triethylamine (2.53 g), and the mixture was refluxed for 4.5 hours under nitrogen. The mixture was cooled and poured into a mixture of ethyl acetate and ice water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (831 mg).

IR (KBr) : 3238, 3061, 3028, 2959, 2924, 2870, 1641, 1564, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.46 (3H, s), 4.49

(4H, br s), 6.6-6.7 (1H, m), 6.90 (1H, s), 7.2-7.8 (10H, m), 8.29 (1H, br s), 12.88 (1H, br s)

APCI-MASS (m/z) : 490 ($M+H^+$)

Example 10

The mixture of N-cycloheptyl-3-(1-tritylpyrazol-3-yl)-benzylamine (14.63 g) and phenyl N-(2,4,6-trifluorophenyl)carbamate (7.64 g) and triethylamine (20 ml) in toluene (360 ml) was stirred at 100°C for one hour. After cooling to room temperature, the reaction mixture was washed with water, aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (700 g, eluting with n-hexane - ethyl acetate (4:1 to 3:1)) to give 1-cycloheptyl-1-[3-(1-tritylpyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea (19.6 g).

IR (KBr) : 2900-3600 (br), 2927, 2858, 1635, 1607, 1520, 1446 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 4.26-4.48 (1H, m), 4.55 (2H, s), 5.57 (1H, s), 6.52-6.70 (3H, m), 6.75-6.97 (2H, m), 7.10-7.45 (16H, m), 7.68-7.80 (2H, m)

Example 11

The following compounds were obtained according to similar manners to those of Examples 7, 8, 9 and 10.

(1) 1-Cyclohexyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3377, 3084, 3057, 2927, 2856, 1653, 1566, 1533, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.8 (10H, m), 2.39 (6H, s), 2.45 (3H, s), 3.85-4.05 (1H, m), 4.47 (2H, s), 6.86 (1H, s), 6.93 (2H, d, J=8.5Hz), 6.95-7.05 (2H, m), 7.35 (2H, d, J=8.5Hz), 7.88 (1H, s)

APCI-MASS (m/z) : 526 ($M+H^+$)

(2) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3307, 3062, 3029, 2999, 2922, 1735, 1660, 1564, 1497 cm^{-1}
NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.46 (3H, s), 4.43 (2H, s), 4.46 (2H, s), 6.89 (1H, s), 6.9-7.4 (13H, m), 8.26 (1H, s)
APCI-MASS (m/z) : 526 ($M+H^+$)

(3) 1-Cycloheptyl-1-(4-phenoxybenzyl)-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3371, 2922, 2856, 1653, 1485, 1219 cm^{-1}
NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 2.36 (3H, s), 2.45 (3H, s), 2.46 (3H, s), 4.22-4.42 (1H, m), 4.55 (2H, s), 5.49 (1H, s), 6.59 (1H, s), 6.95-7.15 (5H, m), 7.24-7.46 (4H, m)
APCI-MASS (m/z) : 522 ($M+H^+$)

(4) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3377, 2924, 2852, 1668, 1481, 1238 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.37 (3H, s), 2.46 (3H, s), 2.47 (3H, s), 4.25-4.40 (1H, m), 4.55 (2H, s), 5.47 (1H, s), 6.60 (1H, s), 6.80-7.08 (4H, m), 7.35-7.50 (4H, m)
APCI-MASS (m/z) : 600, 602 ($M+H^+$)

(5) 1-Benzyl-1-[4-(4-bromophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3200-3700 (br), 2922, 1662, 1564, 1481, 1236 cm^{-1}
NMR ($CDCl_3$, δ) : 2.39 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 4.61 (2H, s), 4.63 (2H, s), 5.68 (1H,

s), 6.62 (1H, s), 6.82-7.05 (4H, m), 7.25-7.50 (9H, m)

APCI-MASS (m/z) : 594, 596 ($M+H^+$)

(6) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-[2,4-dimethoxy-6-methylpyridin-3-yl]urea

IR (KBr) : 3100-3700 (br), 2926, 2856, 1668, 1597, 1504, 1481, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.38 (3H, s), 3.79 (3H, s), 3.83 (3H, s), 4.25-4.40 (1H, m), 4.52 (2H, s), 5.43 (1H, s), 6.36 (1H, s), 6.82-7.06 (4H, m), 7.32-7.50 (4H, m)

APCI-MASS (m/z) : 568, 570 ($M+H^+$)

(7) 1-Benzyl-1-[4-(4-bromophenoxy)benzyl]-3-[2,4-dimethoxy-6-methylpyridin-3-yl]urea

IR (KBr) : 3200-3400 (br), 2997, 1637, 1595, 1506, 1365 cm^{-1}

NMR ($CDCl_3$, δ) : 2.39 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 4.60 (4H, s), 5.64 (1H, s), 6.38 (1H, s), 6.80-7.05 (4H, m), 7.22-7.50 (8H, m)

APCI-MASS (m/z) : 562, 564 ($M+H^+$)

Example 12

To a mixture of 1-cycloheptyl-1-[3-(1-tritylpyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea (17.6 g) and anisole (35 ml) was added trifluoroacetic acid (70 ml). The mixture was stirred at 60°C for 3 hours and cooled to room temperature. The excess trifluoroacetic acid was removed in vacuo. To the residue was added water and ethyl acetate. The mixture was basified with 5N-sodium hydroxide under ice cooling and extracted with ethyl acetate. The organic layer was washed with water, and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (530 g,

eluting with n-hexane - ethyl acetate (2:1 to 1:2)) to give 1-cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea (10.71 g).

IR (KBr) : 3500-2600 (br), 2927, 2858, 1635, 1520, 1448, 1248, 1120 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.10 (12H, m), 4.26-4.46 (1H, m), 4.59 (2H, s), 5.63 (1H, s), 6.53-6.73 (3H, m), 7.30-7.50 (2H, m), 7.63 (1H, d, J=2.3Hz), 7.65-7.80 (2H, m)

APCI-MASS (m/z) : 443 ($M+H^+$)

Examle 13

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)-benzylamine (1.57 g) in toluene (100 ml) were added 3-phenoxycarbonylamino-2,4,6-trimethylpyridine (2.56 g) and triethylamine (1.52 g), and the mixture was refluxed for 3 hours under nitrogen. The mixture was cooled and poured into a mixture of ethyl acetate and water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea (1.83 g).

IR (KBr) : 3313, 2924, 2856, 1630, 1603, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.06 (3H, s), 2.24 (3H, s), 4.05-4.25 (1H, m), 4.48 (2H, s), 6.98 (1H, s), 6.9-7.1 (4H, m), 7.2-7.4 (4H, m), 7.66 (1H, s)

APCI-MASS (m/z) : 476 ($M+H^+$)

Example 14

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)-benzylamine (2.51 g) in toluene (120 ml) were added 4-chloro-6-methyl-2-methylthio-3-phenoxycarbonylaminopyridine (2.47 g) and triethylamine (2.43 g) at room temperature and

the mixture was refluxed for 2.5 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)-benzyl]-3-(2-chloro-6-methyl-4-methylthiopyridin-3-yl)urea (2.76 g).

IR (KBr) : 3371, 3299, 2924, 2852, 1655, 1576, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.8 (12H, m), 2.43 (6H, s), 4.0-4.2 (1H, m), 4.46 (2H, s), 6.9-7.5 (9H, m), 8.07 (1H, br s)

Example 15

To a solution of N-benzyl-3-(pyrazol-3-yl)benzylamine (54.0 g) and triethylamine (143 ml) in toluene (1.35 l) was added 2,4-bis(methylthio)-3-phenoxycarbonylamino-6-methylpyridine (62.4 g) at room temperature and stirred for 24 hours. The resulting precipitate was collected by filtration and recrystallized from dichloromethane - methanol - n-hexane to give 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (51.0 g).

mp : 209-210°C

IR (KBr) : 3392, 3246, 2918, 1649, 1489, 1228, 1093 cm^{-1}

NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.47 (3H, s), 4.49 (4H, s), 6.66 (1H, br s), 6.90 (1H, s), 7.18-7.90 (10H, m), 8.30 (1H, s), 12.89, 13.30 (total 1H, each br)

APCI-MASS (m/z) : 490 ($M+H^+$)

Example 16

To a solution of N-benzyl-[4-(4-bromophenoxy)benzyl]-

amine (1.84 g) and 2,4,6-trimethylphenyl-3-phenoxycarbonylaminopyridine (2.20 g) in N,N-dimethylformamide (50 ml) was added triethylamine (2.53 g), and the mixture was stirred at 150°C for 3 hours under nitrogen. The mixture was cooled and ethyl acetate (150 ml) was added thereto. The insoluble materials were filtered off, and the filtrate was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-benzyl-1-[4-(4-bromophenoxy)-benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea (2.51 g).

IR (KBr) : 3406, 3313, 2929, 2856, 1714, 1632, 1572, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08 (3H, s), 2.26 (3H, s), 2.35 (3H, s), 4.53 (2H, s), 4.57 (2H, s), 6.95-7.15 (5H, m), 7.3-7.6 (9H, m), 8.05 (1H, br s)

APCI-MASS (m/z) : 531 ($M+H^+$)

Example 17

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)-benzylamine (1.25 g) in toluene (80 ml) were added 4,6-bis(methylthio)-2-methyl-5-phenoxycarbonylaminopyrimidine (1.29 g) and triethylamine (1.21 g), and the mixture was refluxed for 2 hours under nitrogen. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]urea (1.33 g).

IR (KBr) : 3255, 2926, 2856, 1653, 1522, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.43 (6H, s), 2.56 (3H, s), 3.95-4.1 (1H, m), 4.46 (2H, s), 6.9-7.4 (8H, m), 8.00 (1H, br s)

APCI-MASS (m/z) : 529 ($M+H^+$)

Example 18

To a solution of 1-cycloheptyl-1-[4-(3,5-di-tert-butyl-4-methoxymethoxyphenoxy)]benzyl-3-(2,4,6-trimethylphenyl)urea (860 mg) in methanol (8.6 ml) was added conc. hydrochloric acid (0.91 ml), and the mixture was stirred at room temperature for 2 hours and at 40°C for 3.5 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and neutralized by addition of saturated sodium bicarbonate aqueous solution. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(3,5-di-tert-butyl-4-hydroxyphenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea (495 mg).

IR (KBr) : 3639, 3404, 3323, 2956, 2923, 2860, 1651, 1593, 1504 cm^{-1}

NMR ($CDCl_3$, δ) : 1.41 (18H, s), 1.5-2.1 (12H, m), 1.98 (6H, s), 2.22 (3H, s), 4.25-4.4 (1H, m), 4.45 (2H, s), 5.03 (1H, s), 6.80 (2H, s), 6.86 (2H, s), 6.93 (2H, d, J=8.5Hz), 7.35 (2H, d, J=8.5Hz)

APCI-MASS (m/z) : 585 ($M+H^+$)

Example 19

To a solution of 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (22.11 g) in dichloromethane (150 ml) was added dropwise a solution of m-chloroperbenzoic acid (26.51 g) in dichloromethane (600 mg) at room temperature over 2 hours. The mixture was stirred at room temperature for 23 hours. The precipitates were removed by filtration and the filtrate was washed with dilute sodium bicarbonate aqueous solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was

purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylsulfonyl)-6-methylpyridin-3-yl]urea (20.42 g).

IR (KBr) : 3361, 3074, 3041, 3016, 2927, 2860, 1740, 1664, 1500, 1325, 1159, 1128 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.2 (12H, m), 2.66 (3H, s), 3.19 (3H, s), 3.30 (3H, s), 4.55 (2H, s), 6.95-7.05 (6H, m), 7.34 (2H, d, J=8.6Hz) 7.26 (1H, s), 7.85 (1H, s)

APCI-MASS (m/z) : 604 ($M+H^+$)

Example 20

To a solution of 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (4.75 g) in dichloromethane (50 ml) was added dropwise a solution of m-chloroperbenzoic acid (3.96 g) in dichloromethane (80 ml) at room temperature. The mixture was stirred at room temperature for 20 hours. The mixture was washed with dilute sodium bicarbonate aqueous solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylsulfinyl)-6-methylpyridin-3-yl]urea (2.15 g).

IR (KBr) : 3251, 2927, 2858, 1738, 1651, 1498, 1055, 1036 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 2.59 (3H, s), 2.82 and 2.94 (total 3H, s), 2.98 (3H, s), 4.0-4.2 (2H, m), 4.51 (2H, br s), 6.9-7.1 (7H, m), 7.25-7.35 (2H, m), 7.77-7.79 (total 1H, s)

APCI-MASS (m/z) : 572 ($M+H^+$)

Example 21

To a suspension of 1-cycloheptyl-1-[3-(1-tritylpyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

(800 mg) in anisole (2 ml) was added trifluoroacetic acid (6 ml) and the mixture was stirred at 100°C for 2 hours. The mixture was evaporated in vacuo and poured into a mixture of ethyl acetate and water and adjusted to pH ca. 9 by addition of sodium hydroxide aqueous solution. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[3-(pyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea (102 mg).

IR (KBr) : 3400, 3207, 2926, 2856, 1635, 1608, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.1-4.3 (1H, m), 4.51 (2H, s), 6.83 (2H, s), 7.1-7.5 (5H, m), 7.84 (1H, s), 8.11 (1H, s), 12.95 (1H, br s)

APCI-MASS (m/z) : 431 ($M+H^+$)

Example 22

The following compounds were obtained according to a similar manner to that of Example 1, 2, 3 or 4.

(1) 1-Cycloheptyl-1-[4-(4-chlorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3410, 2920, 2850, 1660, 1590, 1505, 1485 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.00 (6H, s), 2.22 (3H, s), 4.3-4.45 (1H, m), 4.48 (2H, s), 5.6-5.8 (1H, br), 6.81 (2H, s), 6.92 (2H, d, J=8.5Hz), 7.00 (2H, d, J=8.5Hz), 7.28 (2H, d, J=8.4Hz), 7.38 (2H, d, J=8.4Hz)

(2) 1-Cycloheptyl-1-[4-(3-fluorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

mp : 127-128°C

IR (KBr) : 2924, 2856, 1624, 1605, 1506, 1485 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 2.01 (6H, s), 2.22 (3H, s), 4.30-4.50 (1H, m), 4.50 (2H, s), 5.46 (1H, s), 6.60-6.88 (3H, m), 6.79 (2H, s), 7.00-7.10 (2H, m), 7.20-7.35 (1H, m), 7.36-7.47 (2H, m)

APCI-MASS (m/z) : 475 ($M+H^+$)

(3) 1-Cycloheptyl-1-[4-(4-trifluoromethylphenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

mp : 146-147°C

IR (KBr) : 2924, 2856, 1628, 1504, 1327, 1246 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.03 (6H, s), 2.23 (3H, s), 4.30-4.50 (1H, m), 4.51 (2H, s), 5.47 (1H, s), 6.83 (2H, s), 6.95-7.13 (4H, m), 7.35-7.50 (2H, m), 7.53-7.65 (2H, m)

APCI-MASS (m/z) : 525 ($M+H^+$)

(4) 1-Cycloheptyl-1-[4-(3,4-methylenedioxyphenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

mp : 125-126°C

IR (KBr) : 3323, 2922, 2854, 1628, 1506, 1481 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 1.99 (6H, s), 2.22 (3H, s), 4.33-4.50 (1H, m), 4.46 (2H, s), 5.46 (1H, s), 5.98 (2H, s), 6.47 (1H, dd, J=8.3, 2.4Hz), 6.56 (1H, d, J=2.4Hz), 6.76 (1H, d, J=8.3Hz), 6.81 (2H, s), 6.90-7.00 (2H, m), 7.28-7.38 (2H, m)

APCI-MASS (m/z) : 501 ($M+H^+$)

(5) 1-Cycloheptyl-1-[4-(3,5-di-tert-butyl-4-methoxymethoxyphenoxy)]benzyl-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3406, 3323, 2956, 2924, 2862, 1641, 1589, 1504 cm^{-1}

NMR ($CDCl_3$, δ) : 1.41 (18H, s), 1.4-2.2 (14H, m), 1.99 (6H, s), 2.22 (3H, s), 3.62 and 3.65 (total 3H, s), 4.3-4.5 (1H, m), 4.46 (2H, s), 4.86 and 4.92 (total 2H, s), 6.80 (2H, s), 6.95-7.1 (4H, m), 7.4-7.5 (2H, m)

(6) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)phenyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3425, 2925, 2860, 1670, 1610, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-1.7 and 1.9-2.1 (12H, m), 2.12 (6H, s), 2.22 (3H, s), 4.45-4.65 (1H, m), 5.30 (1H, br s), 6.82 (2H, s), 7.0-7.3 (8H, m)

APCI-MASS (m/z) : 461 ($M+H^+$)

(7) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3307, 3062, 3030, 2918, 1633, 1608, 1510, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 2.00 (6H, s), 2.22 (3H, s), 4.62 (4H, s), 5.68 (1H, s), 6.82 (2H, s), 6.9-7.1 (6H, m), 7.3-7.45 (7H, m)

APCI-MASS (m/z) : 469 ($M+H^+$)

(8) 1-Pentyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3292, 2958, 2920, 2856, 1632, 1608, 1498 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.3Hz), 1.25-1.45 (4H, m), 1.6-1.8 (2H, m), 2.09 (6H, s), 2.30 (3H, s), 3.39 (2H, t, J=7.4Hz), 4.55 (2H, s), 5.74 (1H, br s), 6.84 (2H, s), 6.9-7.1 (6H, m), 7.30 (2H, d, J=8.4Hz)

APCI-MASS (m/z) : 449 ($M+H^+$)

(9) 1-Cyclohexyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-

trimethylphenyl)urea

IR (KBr) : 3296, 2958, 2922, 2890, 1624, 1520, 1487 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.0 (10H, m), 1.99 (6H, s), 2.22 (3H, s), 4.25-4.45 (1H, m), 4.47 (2H, s), 5.54 (1H, br s), 6.81 (2H, s), 6.9-7.1 (6H, m), 7.35 (2H, d, J=8.5Hz)

APCI-MASS (m/z) : 461 ($M+H^+$)

(10) 1-Cyclopentyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3304, 3074, 2933, 2850, 1657, 1608, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-1.8 and 2.0-2.15 (8H, m), 2.00 (6H, s), 2.22 (3H, s), 4.47 (2H, s), 4.7-4.9 (1H, m), 5.35 (1H, br s), 6.82 (2H, s), 6.9-7.1 (6H, m), 7.33 (2H, d, J=8.5Hz)

APCI-MASS (m/z) : 447 ($M+H^+$)

(11) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trifluorophenyl)urea

IR (KBr) : 3284, 2929, 2858, 1633, 1612, 1518, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 4.25-4.45 (1H, m), 4.50 (2H, s), 5.58 (1H, s), 6.55-6.7 (2H, m), 6.9-7.1 (6H, m), 7.25-7.4 (2H, m)

APCI-MASS (m/z) : 487 ($M+H^+$)

(12) 1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3404, 3207, 3060, 3029, 2967, 2918, 2858, 1635, 1608, 1510 cm^{-1}

NMR ($DMSO-d_6$, δ) : 2.09 (6H, s), 2.21 (3H, s), 4.57 (2H, s), 6.0-6.05 (1H, m), 6.84 (2H, s), 7.2-7.5 (7H, m), 7.65-7.8 (3H, m), 7.87 (1H, s), 12.89

(1H, br)
APCI-MASS (m/z) : 425 ($M+H^+$)

(13) 1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3246, 1637, 1522 cm^{-1}
NMR (DMSO-d_6, δ) : 4.54 (4H, s), 6.65 (1H, br s), 7.2-7.5 (4H, m), 7.7-7.9 (3H, m), 8.47 (1H, br s), 12.90 and 13.34 (total 1H, br s)
APCI-MASS (m/z) : 437 ($M+H^+$)

(14) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 3226, 3062, 2927, 2858, 1635, 1612, 1518 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 4.0-4.2 (1H, m), 4.55 (2H, s), 6.63 (1H, d, J=1.9Hz), 7.15-7.5 (4H, m), 7.6-7.8 (3H, m), 8.10 (1H, br s)
APCI-MASS (m/z) : 444 ($M+H^+$)

(15) 1-Cyclohexyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3226, 2929, 2856, 1635, 1608, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.8 (10H, m), 2.08 (6H, s), 2.20 (3H, s), 4.0-4.2 (1H, m), 4.57 (2H, s), 6.62 (1H, br s), 6.83 (2H, s), 7.2-7.45 (2H, m), 7.55-7.85 (3H, m), 12.86 (1H, br s)
APCI-MASS (m/z) : 417 ($M+H^+$)

(16) 1-Cyclopentyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3188, 2956, 2870, 1635, 1608, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.45-4.6 (1H, m), 4.56 (2H, s), 6.63 (1H, br s), 6.83 (2H, s), 7.15-7.45 (2H, m),

7.55-7.85 (5H, m), 12.87 (1H, br s)
APCI-MASS (m/z) : 403 ($M+H^+$)

(17) 1-Cycloheptyl-1-[3-(1-tritylpyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3408, 3323, 3059, 3030, 2924, 2856, 1645, 1608, 1562 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.00 (6H, s), 2.20 (3H, s), 4.0-4.2 (1H, m), 4.48 (2H, s), 6.80 (2H, s), 7.1-7.5 (19H, m), 7.70 (1H, s), 8.02 (1H, s)
APCI-MASS (m/z) : 673 ($M+H^+$)

(18) 1-Cycloheptyl-1-[4-(1-tritylpyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3406, 3323, 3057, 3030, 2924, 2854, 1640, 1568 cm^{-1}
NMR (DMSO-d_6, δ) : 1.40-2.0 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.05-4.25 (1H, m), 4.47 (2H, s), 6.83 (2H, s), 7.05-7.15 (5H, m), 7.25 (2H, d, J=8.2Hz), 7.3-7.4 (11H, m), 7.49 (2H, d, J=8.2Hz), 7.78 (1H, s), 8.07 (1H, s)
APCI-MASS (m/z) : 673 ($M+H^+$)

(19) 1-Cycloheptyl-1-[3-(1-methylpyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3408, 2924, 2856, 1637, 1610, 1497, 1234 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 1.98 (6H, s), 2.20 (3H, s), 3.95 (3H, s), 4.36-4.56 (1H, m), 4.52 (2H, s), 5.48 (1H, s), 6.78 (2H, s), 7.20-7.52 (4H, m), 7.62 (1H, s), 7.75 (1H, s)
APCI-MASS (m/z) : 445 ($M+H^+$)

(20) 1-Cycloheptyl-1-[3-(1-methylpyrazol-3-yl)benzyl]-3-

(2,4,6-trimethylphenyl)urea
mp : 142-143°C
IR (KBr) : 3346, 2924, 2854, 1630, 1502, 1246 cm^{-1}
NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 1.97 (6H, s), 2.19 (3H, s), 3.95 (3H, s), 4.38-4.58 (1H, m), 4.55 (2H, s), 5.49 (1H, s), 6.53 (1H, d, J=2.2Hz), 6.77 (2H, s), 7.30-7.50 (3H, m), 7.65-7.88 (2H, m)
APCI-MASS (m/z) : 445 ($M+H^+$)

(21) 1-Cycloheptyl-1-[3-(1-methylpyrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 171-172°C
IR (KBr) : 3307, 2924, 2856, 1626, 1506, 1254 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 2.00 (6H, s), 2.21 (3H, s), 3.89 (3H, s), 4.30-4.50 (1H, m), 4.57 (2H, s), 5.46 (1H, s), 6.29 (1H, d, J=1.9Hz), 6.80 (2H, s), 7.25-7.56 (5H, m)
APCI-MASS (m/z) : 445 ($M+H^+$)

(22) 1-Cycloheptyl-1-[3-(imidazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3140 (br), 2924, 2856, 1635, 1608, 1497 cm^{-1}
NMR (DMSO-d_6, δ) : 1.25-1.90 (12H, m), 2.07 (6H, s), 2.20 (3H, s), 4.07-4.27 (1H, m), 4.52 (2H, s), 6.82 (2H, s), 7.08-7.80 (7H, m), 12.13, 12.53 (total 1H, each br)
APCI-MASS (m/z) : 431 ($M+H^+$)

(23) 1-Cycloheptyl-1-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 123-124°C
IR (KBr) : 3319, 2924, 2856, 1622, 1500, 1248 cm^{-1}
NMR ($CDCl_3$, δ) : 1.35-2.10 (12H, m), 2.04 (6H, s), 2.22 (3H, s), 2.62 (3H, s), 4.20-4.40 (1H, m),

4.58 (2H, s), 5.58 (1H, s), 6.81 (2H, s), 7.49-7.59 (2H, m), 7.98-8.08 (2H, m)
APCI-MASS (m/z) : 447 ($M+H^+$)

(24) 1-Cycloheptyl-1-[4-(5-methyl-4H-1,2,4-triazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 142-145°C
IR (KBr) : 2600-3700 (br), 2924, 2856, 1633, 1608, 1558, 1504, 1238 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.15 (12H, m), 1.90 (6H, s), 2.27 (3H, s), 2.16 (3H, s), 4.37-4.57 (1H, m), 4.58 (2H, s), 5.59 (1H, s), 6.71 (2H, s), 7.45-7.57 (2H, m), 8.05-8.17 (2H, m)
APCI-MASS (m/z) : 446 ($M+H^+$)

(25) 1-Cycloheptyl-1-[4-(4-benzyl-5-methyl-4H-1,2,4-triazol-3-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 193-194°C
IR (KBr) : 3296, 2924, 2856, 1626, 1506, 1252, 847 cm^{-1}
NMR ($CDCl_3$, δ) : 1.35-2.05 (12H, m), 2.00 (6H, s), 2.21 (3H, s), 2.39 (3H, s), 4.20-4.40 (1H, m), 4.55 (2H, s), 5.15 (2H, s), 5.43 (1H, s), 6.80 (2H, s), 6.90-7.05 (2H, m), 7.30-7.60 (7H, m)
APCI-MASS (m/z) : 536 ($M+H^+$)

(26) 1-Cycloheptyl-1-[3-(2-methyl-2H-tetrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 175-176°C
IR (KBr) : 3327, 2922, 2856, 1628, 1500, 1255 cm^{-1}
NMR (DMSO-d_6, δ) : 1.30-1.90 (12H, m), 2.09 (6H, s), 2.20 (3H, s), 4.12-4.30 (1H, m), 4.42 (3H, s), 4.59 (2H, s), 6.83 (2H, s), 7.40-7.65 (3H, m), 7.85-7.95 (1H, m), 8.06 (1H, s)
APCI-MASS (m/z) : 447 ($M+H^+$)

(27) 1-Cycloheptyl-1-[3-(1-methyl-1H-tetrazol-5-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 171-173°C
IR (KBr) : 3323, 2924, 2854, 1626, 1502, 1444, 1254 cm^{-1}
NMR (DMSO-d_6, δ) : 1.40-1.90 (12H, m), 2.06 (6H, s), 2.20 (3H, s), 4.16 (3H, s), 4.10-4.28 (1H, m), 4.59 (2H, s), 6.83 (2H, s), 7.54-7.80 (5H, m)
APCI-MASS (m/z) : 447 ($M+H^+$)

(28) 1-Cycloheptyl-1-[4-(1,2,4-1H-triazol-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3310, 2924, 2856, 1639, 1518, 1277, 1147 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.07 (6H, s), 2.22 (3H, s), 4.20-4.40 (1H, m), 4.58 (2H, s), 5.49 (1H, s), 6.82 (2H, s), 7.50-7.60 (2H, m), 7.64-7.74 (2H, m), 8.11 (1H, s), 8.55 (1H, s)
APCI-MASS (m/z) : 432 ($M+H^+$)

(29) 1-Cycloheptyl-1-[4-(1,2,3-1H-triazol-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3331, 2924, 2856, 1637, 1498, 1319, 1234, 1034 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.07 (6H, s), 2.22 (3H, s), 4.20-4.38 (1H, m), 4.60 (2H, s), 5.55 (1H, s), 6.83 (2H, s), 7.52-7.61 (2H, m), 7.70-7.80 (2H, m), 7.86 (1H, s), 8.00 (1H, s)
APCI-MASS (m/z) : 432 ($M+H^+$)

(30) 1-Cycloheptyl-1-[4-(2H-1,2,3-triazol-2-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
mp : 157-158°C
IR (KBr) : 3311, 2924, 2856, 1626, 1512, 1255, 955, 847 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.10 (12H, m), 2.04 (6H, s), 2.21 (3H, s), 4.25-4.45 (1H, m), 4.57 (2H, s), 5.51 (1H, s), 6.81 (2H, s), 7.48-7.58 (2H, m), 7.82 (2H, s), 8.04-8.14 (2H, m)

APCI-MASS (m/z) : 432 ($M+H^+$)

(31) 1-Cycloheptyl-1-[4-(4-methylpiperazin-1-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3390, 3335, 2925, 2855, 2795, 2360, 1645, 1610, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.05 (6H, s), 2.20 (6H, s), 2.4-2.5 (4H, m), 3.05-3.15 (4H, m), 4.0-4.2 (1H, m), 4.39 (2H, s), 6.82 (2H, s), 6.88 (2H, d, J=8.5Hz), 7.16 (2H, d, J=8.5Hz), 7.34 (1H, br s)

APCI-MASS (m/z) : 463 ($M+H^+$)

(32) 1-Cycloheptyl-1-[4-(4-methylsulfonylaminophenyl)-benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3400, 3340, 2975, 2925, 2860, 1640, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 3.01 (3H, s), 4.1-4.3 (1H, m), 4.53 (2H, s), 6.83 (2H, s), 7.27 (2H, d, J=8.4Hz), 7.37 (2H, d, J=8.4Hz), 7.53 (1H, br s), 7.55-7.7 (4H, m), 9.82 (1H, s)

APCI-MASS (m/z) : 534 ($M+H^+$)

(33) 1-Cycloheptyl-1-[4-[2-(1-trityl-1H-tetrazol-5-yl)phenyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3407, 3058, 3026, 2924, 2856, 1647, 1608, 1493 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.8 (12H, m), 2.04 (6H, s), 2.20 (3H, s), 4.05-4.25 (1H, m), 4.48 (2H, s), 6.83 (2H, s), 7.04 (2H, d, J=7.9Hz), 7.23 (2H, d,

J=7.9Hz), 7.5-7.8 (5H, m)
FAB-MASS (m/z) : 751 ($M+H^+$)

(34) 1-Cycloheptyl-1-[4-(N-benzoylsulfamoyl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3415, 3361, 2924, 2858, 1632, 1593, 1549 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-2.0 (12H, m), 2.07 (6H, s), 2.20 (3H, s), 4.1-4.3 (1H, m), 4.51 (2H, s), 6.81 (2H, s), 7.2-7.4 (5H, m), 7.53 (1H, br s), 7.76 (2H, d, J=8.0Hz), 7.88 (2H, d, J=8.0Hz)
APCI-MASS (m/z) : 548 ($M+H^+$)

(35) 1-Cycloheptyl-1-[4-(N-phenylsulfonylcarbamoyl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3380, 3290, 3055, 2920, 2855, 1690, 1625, 1610, 1505 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.8 (12H, m), 2.07 (6H, s), 2.21 (3H, s), 4.1-4.25 (1H, m), 4.53 (2H, s), 6.83 (2H, s), 7.38 (2H, d, J=8.2Hz), 7.65-7.8 (4H, m), 7.82 (2H, d, J=8.2Hz), 8.00 (2H, d, J=6.7Hz)
APCI-MASS (m/z) : 548 ($M+H^+$)

(36) 1-Cycloheptyl-1-[4-(3-pyridylmethyl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3412, 3304, 3028, 2920, 2854, 1626, 1502 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 1.95 (6H, s), 2.21 (3H, s), 3.98 (2H, s), 4.35-4.55 (1H, m), 4.48 (2H, s), 5.42 (1H, s), 6.79 (2H, s), 7.19 (2H, d, J=7.7Hz), 7.15-7.25 (1H, m), 7.35 (2H, d, J=7.7Hz), 7.4-7.5 (1H, m), 8.4-8.5 (2H, m)
APCI-MASS (m/z) : 456 ($M+H^+$)

(37) 1-Cycloheptyl-1-[4-(4-pyridylmethyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3408, 3304, 3024, 2922, 2856, 1632, 1605, 1512 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 1.95 (6H, s), 2.21 (3H, s), 3.96 (2H, s), 4.35-4.5 (1H, m), 4.48 (2H, s), 5.42 (1H, s), 6.79 (2H, s), 7.09 (2H, dd, J=6.0, 1.6Hz), 7.20 (2H, d, J=8.1Hz), 7.37 (2H, d, J=8.1Hz), 8.49 (2H, dd, J=6.0, 1.6Hz)

APCI-MASS (m/z) : 456 ($M+H^+$)

(38) 1-Cycloheptyl-1-(3-benzylbenzyl)-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3223, 3025, 2922, 2854, 1626, 1506 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (12H, m), 1.95 (6H, s), 2.21 (3H, s), 3.97 (2H, s), 4.46 (2H, s), 4.3-4.5 (1H, m), 5.42 (1H, s), 6.79 (2H, s), 7.1-7.35 (9H, m)

APCI-MASS (m/z) : 455 ($M+H^+$)

(39) 1-Cycloheptyl-1-[4-(pyrazol-1-ylmethyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

mp : 150-151°C

IR (KBr) : 3307, 2922, 2856, 1628, 1508, 1250, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.05 (12H, m), 1.97 (6H, s), 2.21 (3H, s), 4.30-4.45 (1H, m), 4.49 (2H, s), 5.32 (2H, s), 5.39 (1H, s), 6.28 (1H, dd, J=2.0, 2.0Hz), 6.79 (2H, s), 7.15-7.28 (2H, m), 7.32-7.42 (3H, m), 7.55 (1H, d, J=2.0Hz)

APCI-MASS (m/z) : 445 ($M+H^+$)

(40) 1-Cycloheptyl-1-[4-(imidazol-1-ylmethyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3329 (br), 2924, 2856, 1637, 1504, 1234, 849, 735 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.05 (12H, m), 1.99 (6H, s), 2.21 (3H, s), 4.25-4.45 (1H, m), 4.51 (2H, s), 5.12 (2H, s), 5.40 (1H, s), 6.80 (2H, s), 6.89 (1H, s), 7.10 (1H, s), 7.13-7.23 (2H, m), 7.35-7.45 (2H, m), 7.61 (1H, s)

APCI-MASS (m/z) : 445 ($M+H^+$)

(41) 1-Cycloheptyl-1-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3313, 2924, 2858, 1740, 1643, 1610, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.15 (3H, s), 1.3-2.1 (16H, m), 2.55-2.65 (1H, m), 1.92 (3H, s), 1.99 (3H, s), 2.02 (6H, s), 2.03 (3H, s), 2.21 (3H, s), 3.53 (2H, br s), 6.83 (2H, s), 7.44 (1H, br s)

APCI-MASS (m/z) : 493 ($M+H^+$)

(42) 1-Cycloheptyl-1-[4-[N-(3,5-di-tert-butyl-4-hydroxyphenyl)carbamoyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3639, 3417, 3321, 2951, 2924, 2860, 1643, 1610, 1502 cm^{-1}

NMR (DMSO-d_6, δ) : 1.39 (18H, s), 1.4-1.9 (12H, m), 2.10 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.57 (2H, s), 6.78 (1H, s), 6.85 (2H, s), 7.41 (2H, d, J=8.3Hz), 7.90 (2H, d, J=8.3Hz), 7.44 (2H, s), 7.59 (1H, br s), 9.87 (1H, br s)

APCI-MASS (m/z) : 612 ($M+H^+$)

(43) 1-Cycloheptyl-1-[4-[N-(4-fluorophenyl)carbamoyl]-benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3280, 2926, 2856, 1643, 1610, 1549, 1508 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.11 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.57 (2H, s), 6.85

(2H, s), 7.15-7.3 (2H, m), 7.43 (2H, d, J=8.2Hz), 7.64 (1H, br s), 7.75-7.85 (2H, m), 7.90 (2H, d, J=8.2Hz), 10.22 (1H, s)

APCI-MASS (m/z) : 502 ($M+H^+$)

(44) 1-Cycloheptyl-1-[4-[N-(4-fluorophenyl)-N-methylcarbamoyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3321, 2951, 2923, 2860, 1638, 1606 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.8 (12H, m), 2.01 (6H, s), 2.20 (3H, s), 3.30 (3H, s), 4.0-4.2 (1H, m), 4.42 (2H, s), 6.82 (2H, s), 7.05-7.3 (8H, m), 7.47 (1H, br s)

APCI-MASS (m/z) : 516 ($M+H^+$)

(45) 1-Cycloheptyl-1-[4-[(2,4-dioxothiazolidin-5-yl)methyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 2931, 2858, 2765, 1753, 1709, 1689, 1606, 1632, 1564, 1535, 1502, 1481 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-2.1 (12H, m), 2.05 (6H, s), 2.20 (3H, s), 3.0-3.2 (1H, m), 3.3-3.45 (1H, m), 4.0-4.2 (1H, m), 4.47 (2H, s), 4.85-5.0 (1H, m), 6.82 (2H, s), 7.19 (2H, d, J=8.2Hz), 7.25 (2H, d, J=8.2Hz), 7.44 (1H, br s), 12.3 (1H, br)

APCI-MASS (m/z) : 494 ($M+H^+$)

(46) 1-Cycloheptyl-1-[4-[(2,4-dioxothiazolidin-5-ylidene)methyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3410, 3122, 2924, 2958, 2758, 1743, 1707, 1603, 1504 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.08 (6H, s), 2.21 (3H, s), 4.1-4.3 (1H, m), 4.54 (2H, s), 6.84 (2H, s), 7.44 (2H, d, J=8.3Hz), 7.56 (2H, d, J=8.3Hz), 7.61 (1H, br s), 7.77 (1H, s), 12.60 (1H, br)

APCI-MASS (m/z) : 492 ($M+H^+$)

(47) 1-Cycloheptyl-1-[4-(2-cyanophenyl)benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3410, 3330, 2925, 2855, 2225, 1640, 1610, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-1.8 (12H, m), 2.02 (6H, s), 2.21 (3H, s), 4.35-4.55 (1H, m), 4.58 (2H, s), 5.49 (1H, s), 6.80 (2H, s), 7.4-7.8 (8H, m)

APCI-MASS (m/z) : 466 ($M+H^+$)

Example 23

The following compounds were obtained according to a similar manner to that of Example 7, 8, 9, 10, 13, 14, 15, 16 or 17.

(1) 1-Cycloheptyl-1-[4-(4'-chlorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3371, 2924, 2856, 1662, 1589, 1564, 1506, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-1.9 (12H, m), 2.39 (6H, s), 2.44 (3H, s), 4.0-4.2 (1H, m), 4.46 (2H, s), 6.86 (1H, s), 6.95-7.1 (4H, m), 7.35-7.5 (4H, m), 7.84 (1H, br s)

APCI-MASS (m/z) : 556 ($M+H^+$)

(2) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3313, 2955, 2924, 2872, 1655, 1564, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (8H, m), 2.39 (6H, s), 2.44 (3H, s), 4.3-4.5 (1H, m), 4.47 (2H, s), 6.86 (1H, s), 6.9-7.1 (4H, m), 7.15-7.35 (4H, m), 7.87 (1H, s)

APCI-MASS (m/z) : 512 ($M+H^+$)

(3) 1-Cycloheptyl-1-(3-phenoxybenzyl)-3-[2,4-

bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3294, 2924, 2854, 1740, 1635, 1562, 1483 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-2.0 (12H, m), 2.32 (6H, s), 2.43 (3H, s), 4.0-4.2 (1H, m), 4.47 (2H, s), 6.83 (1H, s), 6.9-7.45 (9H, m), 7.84 (1H, br s)
APCI-MASS (m/z) : 522 ($M+H^+$)

(4) 1-Cycloheptyl-1-[3-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3332, 3066, 2926, 2856, 1664, 1608, 1564, 1497 cm^{-1}
NMR ($CDCl_3$, δ) : 1.45-2.05 (12H, m), 2.34 (3H, s), 2.45 (6H, s), 4.15-4.4 (1H, m), 4.54 (2H, s), 5.46 (1H, s), 6.58 (1H, s), 6.85-7.4 (8H, m)

(5) 1-(4-Dimethylaminobenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
IR (KBr) : 2600-3650 (br), 1635, 1614, 1522, 1448, 1352 cm^{-1}
NMR (DMSO-d_6, δ) : 2.88 (6H, s), 4.38 (2H, s), 4.47 (2H, s), 6.55-6.77 (3H, m), 7.08-7.83 (9H, m), 8.39 (1H, s), 12.89, 13.33 (total 1H, each br)
APCI-MASS (m/z) : 480 ($M+H^+$)

(6) 1-(2,3,5,6-Tetrahydro-4H-pyran-4-yl)-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3294, 3064, 2956, 2926, 2848, 1655, 1562, 1497 cm^{-1}
NMR (DMSO-d_6, δ) : 1.55-1.85 (4H, m), 2.40 (6H, s), 2.45 (3H, s), 3.3-3.5 (2H, m), 3.8-3.9 (2H, m), 4.1-4.3 (1H, m), 4.51 (2H, s), 6.87 (1H, s), 6.9-7.4 (8H, m), 7.98 (1H, br s)

(7) 1-(2-Phenylethyl)-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3294, 3062, 3026, 2924, 1655, 1562, 1497 cm^{-1}
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.48 (3H, s), 2.51 (3H, s), 3.01 (2H, t, J=7.8Hz), 3.61 (2H, t, J=7.8Hz), 4.43 (2H, s), 5.65 (1H, br s), 6.64 (1H, s), 6.9-7.1 (6H, m), 7.2-7.35 (7H, m)
APCI-MASS (m/z) : 548 ($M+H^+$)

(8) 1-(2-Ethoxyethyl)-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3298, 3063, 2976, 2926, 2881, 2856, 1664, 1562, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 1.12 (3H, t, J=6.9Hz), 2.40 (6H, s), 2.45 (3H, s), 3.46 (2H, q, J=6.9Hz), 3.4-3.65 (4H, m), 4.54 (2H, s), 6.87 (1H, s), 6.93-7.4 (8H, m), 7.9 (1H, br s)
APCI-MASS (m/z) : 516 ($M+H^+$)

(9) 1-Benzyl-1-(3-phenoxybenzyl)-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3404, 3032, 2997, 2922, 1668, 1610, 1562, 1500, 1452 cm^{-1}
NMR (DMSO-d_6, δ) : 2.35 (6H, s), 2.43 (3H, s), 4.44 (2H, s), 4.47 (2H, s), 6.86 (1H, s), 6.9-7.45 (14H, m), 8.24 (1H, br s)
APCI-MASS (m/z) : 516 ($M+H^+$)

(10) 1-Benzyl-1-[3-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3298, 3062, 3028, 2922, 1662, 1564, 1498 cm^{-1}
NMR ($CDCl_3$, δ) : 2.36 (3H, s), 2.46 (6H, s), 4.61 (2H, s), 4.62 (2H, s), 5.66 (1H, s), 6.85-7.4

(13H, m)
APCI-MASS (m/z) : 534 ($M+H^+$)

(11) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3211, 3061, 2924, 2856, 1643, 1564, 1531, 1485 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.39 (6H, s), 2.45 (3H, s), 4.0-4.2 (1H, m), 4.52 (2H, s), 6.6-6.7 (1H, m), 6.86 (1H, s), 7.2-7.9 (6H, m), 12.85 (1H, br s)
APCI-MASS (m/z) : 496 ($M+H^+$)

(12) 1-Benzyl-1-[3-(1-methylpyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 165-166°C
IR (KBr) : 3280, 2922, 1643, 1562, 1500, 1435 cm^{-1}
NMR ($CDCl_3$, δ) : 2.36 (3H, s), 2.46 (6H, s), 3.95 (3H, s), 4.66 (4H, s), 5.70 (1H, s), 6.57 (1H, d, J=2.3Hz), 6.61 (1H, s), 7.22-7.45 (8H, m), 7.72-7.80 (2H, m)
FAB-MASS (m/z) : 504 ($M+H^+$)

(13) 1-Benzyl-1-[3-(1-methylpyrazol-5-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3280, 2922, 1649, 1562, 1500, 1431, 1390 cm^{-1}
NMR ($CDCl_3$, δ) : 2.35 (3H, s), 2.45 (3H, s), 2.46 (3H, s), 3.88 (3H, s), 4.64 (2H, s), 4.71 (2H, s), 5.70 (1H, s), 6.32 (1H, d, J=1.9Hz), 6.61 (1H, s), 7.20-7.55 (10H, m)
FAB-MASS (m/z) : 504 ($M+H^+$)

(14) 1-Benzyl-1-[4-(1-methylpyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3305, 2922, 1659, 1564, 1489, 1338, 1227 cm^{-1}

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3.96 (3H, s), 4.63 (4H, s), 5.71 (1H, s), 6.54 (1H, d, J=2.3Hz), 6.62 (1H, s), 7.25-7.47 (8H, m), 7.75-7.85 (2H, m)

APCI-MASS (m/z) : 504 ($M+H^+$)

(15) 1-Benzyl-1-[4-(1-methylpyrazol-5-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3286, 2922, 1657, 1562, 1495, 1389 cm^{-1}

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3.90 (3H, s), 4.66 (2H, s), 4.69 (2H, s), 5.71 (1H, s), 6.31 (1H, d, J=1.9Hz), 6.63 (1H, s), 7.25-7.51 (9H, m), 7.52 (1H, d, J=1.9Hz)

APCI-MASS (m/z) : 504 ($M+H^+$)

(16) 1-Benzyl-1-[4-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

mp : 150-152°C

IR (KBr) : 3400, 3215, 2922, 1649, 1560, 1487, 1228 cm^{-1}

NMR (DMSO-d_6, δ) : 2.44 (6H, s), 2.47 (3H, s), 4.46 (4H, s), 6.72 (1H, s), 6.90 (1H, s), 7.22-7.90 (10H, m), 8.30 (1H, s), 12.87, 13.27 (total 1H, each br)

APCI-MASS (m/z) : 490 ($M+H^+$)

(17) 1-Cycloheptyl-1-[4-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

mp : 174-175°C

IR (KBr) : 2690-3700 (br), 2924, 2856, 1637, 1564, 1484, 1340, 1207, 804 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30-1.90 (12H, m), 2.41 (6H, s), 2.45 (3H, s), 3.95-4.15 (1H, m), 4.49 (2H, s),

6.67 (1H, br s), 6.86 (1H, s), 7.32-7.93 (6H, m), 12.80, 13.19 (total 1H, each br)
APCI-MASS (m/z) : 496 ($M+H^+$)

(18) 1-(4-Methoxybenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 170-173°C
IR (KBr) : 3394, 3250, 3101, 2920, 1664, 1562, 1483, 1223 cm^{-1}
NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.47 (3H, s), 3.75 (3H, s), 4.41 (2H, s), 4.45 (2H, s), 6.67 (1H, br s), 6.88-7.03 (3H, m), 7.13-7.90 (7H, m), 8.27 (1H, s), 12.89, 13.30 (total 1H, each br)
APCI-MASS (m/z) : 520 ($M+H^+$)

(19) 1-(4-Fluorobenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 166-168°C
IR (KBr) : 3390, 3257, 2920, 1653, 1562, 1489, 1227 cm^{-1}
NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.46 (3H, s), 4.47 (2H, s), 4.49 (2H, s), 6.66 (1H, d, J=2.0Hz), 6.90 (1H, s), 7.12-7.45 (6H, m), 7.60-7.90 (3H, m), 8.30 (1H, s), 12.89, 13.30 (total 1H, each br)
APCI-MASS (m/z) : 508 ($M+H^+$)

(20) 1-(4-Dimethylaminobenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 185-188°C
IR (KBr) : 3236, 2922, 1633, 1612, 1524, 1487, 1338, 1219 cm^{-1}
NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.47 (3H, s), 2.89 (6H, s), 4.35 (2H, br s), 4.42 (2H, br s), 6.60-6.76 (3H, m), 6.90 (1H, s), 7.10-7.90 (7H, m),

8.23 (1H, s), 12.89, 13.30 (total 1H, each br)
APCI-MASS (m/z) : 533 ($M+H^+$)

(21) 1-Benzyl-1-[4-(1-methylpyrazol-4-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 224-225°C
IR (KBr) : 3217, 2922, 1655, 1566, 1498, 1456, 1228, 806 cm^{-1}
NMR (DMSO-d_6, δ) : 2.43 (6H, s), 2.47 (3H, s), 3.86 (3H, s), 4.30-4.50 (4H, m), 6.90 (1H, s), 7.20-7.40 (7H, m), 7.50-7.60 (2H, m), 7.86 (1H, s), 8.13 (1H, s), 8.28 (1H, s)
APCI-MASS (m/z) : 504 ($M+H^+$)

(22) 1-Cycloheptyl-1-[4-(1-methylpyrazol-4-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 247-248°C
IR (KBr) : 3188, 2922, 2854, 1641, 1564, 1491, 1213 cm^{-1}
NMR (DMSO-d_6, δ) : 1.30-1.90 (12H, m), 2.40 (6H, s), 2.45 (3H, s), 3.85 (3H, s), 3.90-4.15 (1H, m), 4.45 (2H, s), 6.86 (1H, s), 7.28-7.38 (2H, m), 7.43-7.54 (2H, m), 7.83 (1H, s), 7.85 (1H, br s), 8.10 (1H, s)
APCI-MASS (m/z) : 510 ($M+H^+$)

(23) 1-Benzyl-1-[3-(imidazol-4-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 134-136°C
IR (KBr): 2690-3700 (br), 1637, 1562, 1490, 1228 cm^{-1}
NMR (DMSO-d_6, δ) : 2.43 (6H, s), 2.47 (3H, s), 4.47 (4H, s), 6.90 (1H, s), 7.10-7.75 (11H, m), 8.28 (1H, s), 12.17, 12.55 (total 1H, each br)
APCI-MASS (m/z) : 490 ($M+H^+$)

(24) 1-Benzyl-1-[3-(2-methyl-2H-tetrazol-5-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3290, 2922, 1655, 1562, 1493, 1227, 970, 806 cm^{-1}
NMR ($CDCl_3$, δ) : 2.39 (3H, s), 2.47 (3H, s), 2.48 (3H, s), 4.40 (3H, s), 4.67 (2H, s), 4.72 (2H, s), 5.72 (1H, s), 6.62 (1H, s), 7.25-7.58 (7H, m), 8.01-8.18 (2H, m)
APCI-MASS (m/z) : 506 ($M+H^+$)

(25) 1-Cycloheptyl-1-[4-[(2,4-dioxothiazolidin-5-yl)methyl]benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 2924, 2860, 2769, 1753, 1701, 1603, 1506 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.40 (6H, s), 2.45 (3H, s), 3.07 (1H, dd, J=14.0, 9.4Hz), 3.35 (1H, dd, J=14.0, 4.3Hz), 3.95-4.15 (1H, m), 4.45 (2H, s), 4.90 (1H, dd, J=9.4, 4.3Hz), 6.86 (1H, s), 7.17 (2H, d, J=8.1Hz), 7.30 (2H, d, J=8.1Hz), 7.86 (1H, br s), 12.04 (1H, br)
APCI-MASS (m/z) : 559 ($M+H^+$)

(26) 1-Cycloheptyl-1-[4-[(2,4-dioxothiazolidin-5-ylidene)methyl]benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3406, 3124, 2926, 2856, 2765, 1757, 1711, 1635, 1599, 1487 cm^{-1}
NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.40 (6H, s), 2.45 (3H, s), 4.0-4.2 (1H, m), 4.52 (2H, br s), 6.86 (1H, s), 7.48 (2H, d, J=8.6Hz), 7.54 (2H, d, J=8.6Hz), 7.77 (1H, s), 7.96 (1H, br s), 12.59 (1H, br)
APCI-MASS (m/z) : 557 ($M+H^+$)

(27) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea
IR (KBr) : 3294, 3030, 2922, 1632, 1605, 1498 cm^{-1}
NMR (DMSO-d_6, δ) : 2.08 (3H, s), 2.26 (3H, s), 2.35 (3H, s), 4.52 (2H, s), 4.56 (2H, s), 6.95-7.45 (14H, m), 8.02 (1H, br s)
APCI-MASS (m/z) : 476 ($M+H^+$)

(28) 1-Cyclohexyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea
IR (KBr) : 3406, 3313, 2929, 2856, 1714, 1632, 1605, 1572, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 1.0-1.9 (10H, m), 2.07 (3H, s), 2.24 (3H, s), 2.34 (3H, s), 3.95-4.15 (1H, m), 4.51 (2H, s), 6.95-7.4 (8H, m), 7.70 (1H, s)
APCI-MASS (m/z) : 462 ($M+H^+$)

(29) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea
IR (KBr) : 3310, 1632, 1504, 1483, 1238 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38-2.05 (12H, m), 2.04 (3H, s), 2.20 (3H, s), 2.42 (3H, s), 4.30-4.50 (1H, m), 4.50 (2H, s), 5.49 (1H, s), 6.82 (1H, s), 6.83-6.93 (2H, m), 6.98-7.08 (2H, m), 7.32-7.48 (4H, m)
APCI-MASS (m/z) : 536, 538 ($M+H^+$)

(30) 1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea
IR (KBr) : 3236, 2924, 1645, 1564, 1493 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10 (3H, s), 2.28 (3H, s), 2.35 (3H, s), 4.59 (4H, s), 6.6-6.7 (1H, m), 6.94 (1H, s), 7.2-7.8 (10H, m), 8.07 (1H, br s), 12.89 (1H, br)
APCI-MASS (m/z) : 426 ($M+H^+$)

(31) 1-Cycloheptyl-1-[3-(1-tritylpyrazol-3-yl)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea

IR (KBr) : 3404, 3313, 3059, 3028, 2924, 2856, 1720, 1650, 1605, 1500, 1481 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 1.96 (3H, s), 2.19 (3H, s), 2.33 (3H, s), 4.1-4.3 (1H, m), 4.54 (2H, s), 6.71 (1H, d, J=2.5Hz), 6.85 (1H, s), 7.1-7.8 (20H, m)

FAB-MASS (m/z) : 674 ($M+H^+$)

(32) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-[4,6-bis(methylthio)-2-methylpyridin-5-yl]urea

IR (KBr) : 3275, 3062, 3030, 2926, 1637, 1535, 1479 cm^{-1}

NMR (DMSO-d_6, δ) : 2.46 (6H, s), 2.58 (3H, s), 4.44 (2H, s), 4.48 (2H, s), 6.95-7.4 (13H, m), 8.39 (1H, br s)

APCI-MASS (m/z) : 535 ($M+H^+$)

(33) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]urea

mp : 173-175°C

IR (KBr) : 3375, 2926, 2852, 1668, 1583, 1479, 1238, 810 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.10 (12H, m), 2.48 (6H, s), 2.59 (3H, s), 4.20-4.42 (1H, m), 4.54 (2H, s), 5.40 (1H, s), 6.85-6.93 (2H, m), 7.00-7.10 (2H, m), 7.34-7.50 (4H, m)

APCI-MASS (m/z) : 601, 603 ($M+H^+$)

(34) 1-Benzyl-1-[3-(4-fluorophenoxy)benzyl]-3-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]urea

IR (KBr) : 3271, 3059, 3030, 2926, 2789, 2735, 2605, 1639, 1585, 1533, 1508 cm^{-1}

NMR ($CDCl_3$, δ) : 2.46 (6H, s), 2.58 (3H, s), 4.61

(4H, br s), 5.58 (1H, s), 6.8-7.4 (13H, m)
APCI-MASS (m/z) : 535 ($M+H^+$)

(35) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]urea
mp : 164-165°C
IR (KBr) : 3194, 2926, 2856, 1633, 1518, 1419, 1296, 812 cm^{-1}
NMR (DMSO-d_6, δ) : 1.30-1.90 (12H, m), 2.43 (6H, s), 2.57 (3H, s), 3.95-4.15 (1H, m), 4.53 (2H, s), 6.65 (1H, s), 7.15-7.90 (5H, m), 8.07 (1H, s), 12.86, 13.30 (total 1H, each br)
APCI-MASS (m/z) : 497 ($M+H^+$)

(36) 1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]urea
mp : 212-213°C
IR (KBr) : 3388, 3265, 2924, 1653, 1524, 1487, 1390, 1356, 1298, 1228 cm^{-1}
NMR (DMSO-d_6, δ) : 2.46 (6H, s), 2.58 (3H, s), 4.50 (4H, s), 6.60-6.70 (1H, m), 7.15-7.85 (10H, m), 8.45 (1H, s), 12.89, 13.32 (total 1H, each br s)
APCI-MASS (m/z) : 491 ($M+H^+$)

(37) 1-Benzyl-1-[4-(4'-fluorophenoxy)benzyl]-3-[2,4-dimethoxy-6-methylpyridin-3-yl]urea
IR (KBr) : 3394, 3315, 3062, 2945, 2858, 1660, 1597, 1497 cm^{-1}
NMR (DMSO-d_6, δ) : 1.99 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 4.41 (2H, s), 4.45 (2H, s), 6.67 (1H, s), 6.95-7.45 (13H, m)
APCI-MASS (m/z) : 502 ($M+H^+$)

(38) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-dimethoxy-6-methylpyridin-3-yl]urea

IR (KBr) : 3379, 3207, 3055, 2926, 2856, 1651, 1597, 1502 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.9 (12H, m), 2.35 (3H, s), 3.75 (3H, s), 3.76 (6H, s), 4.0-4.2 (1H, m), 4.50 (2H, s), 6.55 (1H, s), 6.6-6.65 (1H, m), 7.1-7.8 (5H, m), 12.85 (1H, br s)

APCI-MASS (m/z) : 464 ($M+H^+$)

(39) 1-Benzyl-1-[3-(1-tritylpyrazol-3-yl)benzyl]-3-(2,4-dimethoxy-6-methylpyridin-3-yl)urea

IR (KBr) : 3990, 3066, 3032, 2980, 2933, 1678, 1637, 1512, 1497 cm^{-1}

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.72 (3H, s), 3.74 (3H, s), 4.46 (4H, br s), 6.64 (1H, s), 6.73 (1H, d, J=2.5Hz), 7.1-7.7 (24H, m)

(40) 1-(4-Fluorobenzyl)-1-[3-(1-tritylpyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea

IR (KBr) : 3294, 1637, 1608, 1518, 1446, 1225 cm^{-1}

NMR ($CDCl_3$, δ) : 4.58 (2H, s), 4.60 (2H, s), 5.75 (1H, s), 6.54 (1H, d, J=2.5Hz), 6.57-7.10 (6H, m), 7.13-7.43 (18H, m), 7.65-7.80 (2H, m)

(41) 1-Cycloheptyl-1-(4-phenylbenzyl)-3-(2,4,6-trimethylpyridin-3-yl)urea

IR (KBr) : 3402, 3028, 2924, 2854, 1738, 1660, 1603, 1566, 1493 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.09 (3H, s), 2.27 (3H, s), 2.34 (3H, s), 4.05-4.25 (1H, m), 4.55 (2H, s), 6.93 (1H, s), 7.3-7.8 (9H, m)

APCI-MASS (m/z) : 442 ($M+H^+$)

Example 24

The following compounds were obtained according to a

similar manner to that of Example 6, 12 or 21.

(1) 1-Cycloheptyl-1-[4-(pyrazol-4-yl)benzyl]-3-(2,4,6-trimethylphenyl)urea
IR (KBr) : 3184, 2926, 2856, 1630, 1650, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.09 (6H, s), 2.21 (3H, s), 4.05-4.25 (1H, m), 4.48 (2H, s), 6.83 (2H, s), 7.28 (2H, d, J=8.2Hz), 7.50 (1H, br s), 7.56 (2H, d, J=8.2Hz), 7.87 (2H, s)

(2) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-dimethoxy-6-methylpyridin-3-yl)urea
IR (KBr) : 3406, 3228, 3062, 3026, 2974, 1676, 1653, 1597, 1508 cm^{-1}
NMR (DMSO-d_6, δ) : 2.37 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.47 (4H, s), 6.65 (1H, d, J=2.7Hz), 6.66 (1H, s), 7.2-7.5 (7H, m), 7.65-7.8 (4H, m)
APCI-MASS (m/z) : 458 ($M+H^+$)

(3) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea
IR (KBr) : 3400, 3224, 3055, 2929, 2856, 1714, 1633, 1568, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.9 (12H, m), 2.09 (3H, s), 2.26 (3H, s), 2.34 (3H, s), 4.05-4.25 (1H, m), 4.56 (2H, s), 6.6-6.7 (1H, m), 6.91 (1H, s), 7.2-7.5 (2H, m), 7.6-7.9 (3H, m), 12.85 (1H, br s)
APCI-MASS (m/z) : 432 ($M+H^+$)

(4) 1-(4-Fluorobenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-(2,4,6-trifluorophenyl)urea
mp : 204-206°C
IR (KBr) : 3413, 3066, 1664, 1610, 1520, 1223 cm^{-1}
NMR (DMSO-d_6, δ) : 4.51 (2H, s), 4.55 (2H, s), 6.65 (1H, d, J=2.3Hz), 7.10-7.50 (9H, m), 7.55-7.90

(2H, m), 8.46 (1H, s), 12.89, 13.30 (total 1H, each br)

APCI-MASS (m/z) : 455 ($M+H^+$)

(5) 1-Cycloheptyl-1-[4-[2-(1H-tetrazol-5-yl)phenyl]benzyl]-3-(2,4,6-trimethylphenyl)urea

IR (KBr) : 3408, 3310, 2924, 2856, 1620, 1605, 1506 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-1.8 (12H, m), 2.04 (6H, s), 2.20 (3H, s), 4.05-4.25 (1H, m), 4.48 (2H, s), 6.83 (2H, s), 7.04 (2H, d, J=7.9Hz), 7.23 (2H, d, J=7.9Hz), 7.5-7.8 (5H, m)

FAB-MASS (m/z) : 509 ($M+H^+$)

Example 25

To a solution of 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylsulfonyl)-6-methylpyridin-3-yl]urea (3.04 g) in methanol (100 ml) was added sodium methanethiolate (315 mg) and the mixture was stirred at 50°C for an hour under nitrogen. The mixture was cooled to 5°C and the precipitates were collected by filtration, washed with methanol and diisopropyl ether and dried in vacuo to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2-methylsulfonyl-4-methylthio-6-methylpyridin-3-yl)urea (1.35 g) as a crystal.

IR (KBr) : 3377, 3072, 2926, 2858, 1657, 1572, 1498, 1473 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.44 (3H, s), 2.54 (3H, s), 3.23 (3H, s), 4.1-4.3 (1H, m), 4.55 (2H, s), 6.98 (1H, s), 6.9-7.1 (6H, m), 7.35 (1H, d, J=8.6Hz)

Example 26

To a stirred solution of 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

(1 g) in dichloromethane (8 ml) was added a solution of m-chloroperbenzoic acid (1.32 g) in dichloromethane (26 ml) at 0-5°C. After stirring for one hour at room temperature, the mixture was washed with saturated sodium bicarbonate aqueous solution, water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was chromatographed on silica gel to give 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylsulfonyl)-6-methylpyridin-3-yl]urea (183.0 mg) and 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylsulfinyl)-6-methylpyridin-3-yl]urea (235.6 mg).

1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylsulfonyl)-6-methylpyridin-3-yl]urea

IR (KBr) : 3344, 2924, 1655, 1493, 1313, 1238, 1136 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70 (3H, s), 3.32 (6H, s), 4.52 (4H, br s), 6.75 (1H, br s), 7.20-7.85 (10H, m), 8.13 (1H, s), 8.66 (1H, s), 12.87, 13.22 (total 1H, each br)

APCI-MASS (m/z) : 554 ($M+H^+$)

1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylsulfinyl)-6-methylpyridin-3-yl]urea

IR (KBr) : 3217, 2922, 1651, 1495, 1236, 1038, 960 cm^{-1}

NMR (DMSO-d_6, δ) : 2.60-2.80 (9H, m), 4.42-4.75 (4H, m), 6.71 (1H, br s), 7.15-7.85 (11H, m), 8.84, 8.96 (total 1H, each s), 12.93, 13.35 (total 1H, each br)

APCI-MASS (m/z) : 522 ($M+H^+$)

Example 27

To a solution of N-cycloheptyl-4-(4-fluorophenoxy)benzylamine (1.57 g) in toluene (40 ml) were

added 2,4-dichloro-6-methyl-3-phenoxycarbonylaminopyridine (1.49 g) and triethylamine (1.52 g), and the mixture was stirred at 100°C for 3.5 hours. The mixture was poured into a mixture of ethyl acetate and ice water, and the separated organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 1-cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4-dichloro-6-methylpyridin-3-yl)urea (916 mg).

IR (KBr) : 3365, 3275, 3062, 2927, 2858, 1653, 1581, 1543, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.47 (3H, s), 4.2-4.4 (1H, m), 4.53 (2H, s), 5.89 (1H, s), 6.9-7.1 (6H, m), 7.14 (1H, s), 7.36 (2H, d, J=8.7Hz)

APCI-MASS (m/z) : 520, 518, 517 ($M+H^+$)

Example 28

The following compounds were obtained according to a similar manner to that of Example 7, 8, 9, 10, 13, 14, 15, 16, 17 or 27.

(1) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-[(2-methoxy-4-methylthio-6-methyl)pyridin-3-yl]urea

IR (KBr) : 3371, 3064, 2926, 2856, 1666, 1585, 1498 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.1 (12H, m), 2.38 (6H, s), 3.79 (3H, s), 4.2-4.4 (1H, m), 4.52 (2H, s), 5.66 (1H, br s), 6.53 (1H, s), 6.9-7.1 (6H, m), 7.35 (1H, d, J=8.7Hz)

APCI-MASS (m/z) : 524 ($M+H^+$)

(2) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2-chloro-4-methylthio-6-methylpyridin-3-yl)urea

IR (KBr) : 3294, 3061, 3030, 2924, 1651, 1576, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.47 (3H, s), 4.61 (2H, s), 4.63 (2H, s), 5.96 (1H, s), 6.82 (1H, s), 6.9-7.1 (6H, m), 7.25-7.45 (7H, m)

(3) 1-Benzyl-1-[3-(1-methylpyrazol-4-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 137-138°C
IR (KBr) : 3255, 2922, 1651, 1562, 1493, 1228, 982 cm^{-1}
NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.47 (3H, s), 3.87 (3H, s), 4.66 (2H, br s), 4.48 (2H, br s), 6.90 (1H, s), 7.13 (1H, d, J=7.4Hz), 7.20-7.56 (8H, m), 7.81 (1H, s), 8.06 (1H, s), 8.29 (1H, s)
APCI-MASS (m/z) : 504 ($M+H^+$)

(4) 1-Cycloheptyl-1-[3-(1-methylpyrazol-4-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 197-198°C
IR (KBr) : 3290, 2924, 2854, 1653, 1485, 1227 cm^{-1}
NMR (DMSO-d_6, δ) : 1.25-1.90 (12H, m), 2.40 (6H, s), 2.45 (3H, s), 3.87 (3H, s), 3.98-4.17 (1H, m), 4.48 (2H, br s), 6.87 (1H, s), 7.15 (1H, d, J=7.5Hz), 7.27 (1H, dd, J=7.5, 7.5Hz), 7.38 (1H, d, J=7.5Hz), 7.52 (1H, s), 7.80 (1H, s), 7.90 (1H, br s), 8.04 (1H, s)
APCI-MASS (m/z) : 510 ($M+H^+$)

(5) 1-(2-Methoxybenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
IR (KBr) : 3220, 2922, 1649, 1562, 1491, 1240 cm^{-1}
NMR (DMSO-d_6, δ) : 2.41 (6H, s), 2.46 (3H, s), 3.73 (3H, s), 4.44 (2H, br s), 4.53 (2H, br s), 6.67 (1H, br s), 6.88 (1H, s), 6.90-7.05 (2H, m), 7.15-7.90 (7H, m), 8.19 (1H, br s), 12.89, 13.30 (total 1H, each br)

APCI-MASS (m/z) : 520 ($M+H^+$)

(6) 1-(3-Methoxybenzyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 165-166°C
IR (KBr) : 3400, 3248, 3099, 2926, 1664, 1483, 1225, 1049 cm^{-1}
NMR (DMSO-d_6, δ) : 2.41 (6H, s), 2.46 (3H, s), 3.75 (3H, s), 4.46 (2H, br s), 4.50 (2H, br s), 6.58-6.72 (1H, m), 6.74-6.95 (4H, m), 7.15-7.85 (6H, m), 8.28 (1H, s), 12.87, 13.29 (total 1H, each br)
APCI-MASS (m/z) : 520 ($M+H^+$)

(7) 1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2-chloro-4-methylthio-6-methylpyridin-3-yl]urea
IR (KBr) : 3230, 2922, 1647, 1576, 1497, 1338, 1279, 1232 cm^{-1}
NMR (DMSO-d_6, δ) : 2.45 (6H, s), 4.51 (4H, br s), 6.57-6.70 (1H, m), 7.16 (1H, s), 7.17-7.85 (10H, m), 8.52 (1H, s), 12.89, 13.31 (total 1H, each br)
APCI-MASS (m/z) : 478, 480 ($M+H^+$)

(8) 1-(4-Methoxybenzyl)-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea
mp : 130-131°C
IR (KBr) : 3404, 2995, 2924, 2833, 1674, 1610, 1562, 1493, 1250, 1211 cm^{-1}
NMR ($CDCl_3$, δ) : 2.39 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 3.81 (3H, s), 4.56 (2H, s), 4.58 (2H, s), 5.72 (1H, s), 6.64 (1H, s), 6.85-7.12 (8H, m), 7.20-7.38 (4H, m)
APCI-MASS (m/z) : 564 ($M+H^+$)

(9) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4-dichloro-6-methylpyridin-3-yl)urea

IR (KBr) : 3302, 3066, 3032, 2924, 1639, 1581, 1543, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 4.63 (2H, s), 4.64 (2H, s), 6.05 (1H, br s), 6.9-7.4 (14H, m),

APCI-MASS (m/z) : 514, 512, 510 ($M+H^+$)

(10) 1-(3-Phenylpropyl)-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3290, 2922, 1649, 1562, 1497, 1211, 1093 cm^{-1}

NMR ($CDCl_3$, δ) : 1.92-2.13 (2H, m), 2.38 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 2.68 (2H, t, J=7.7Hz), 3.39 (2H, t, J=7.6Hz), 4.57 (2H, s), 5.57 (1H, s), 6.63 (1H, s), 6.87-7.10 (6H, m), 7.10-7.37 (7H, m)

APCI-MASS (m/z) : 562 ($M+H^+$)

(11) 1-(2-Phenylethyl)-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3209 (br), 2922, 1647, 1562, 1491, 1338, 1238 cm^{-1}

NMR (DMSO-d_6, δ) : 2.42 (6H, s), 2.47 (3H, s), 2.80-2.98 (2H, m), 3.35-3.54 (2H, m), 4.44 (2H, s), 6.65 (1H, br s), 6.90 (1H, s), 7.10-7.45 (7H, m), 7.45-7.83 (3H, m), 8.13 (1H, s), 12.87, 13.30 (total 1H, each br)

APCI-MASS (m/z) : 504 ($M+H^+$)

(12) 1-[(S)-1-Phenylethyl]-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3373, 3310, 2978, 2924, 1660, 1562, 1497, 1246, 1211 cm^{-1}

NMR ($CDCl_3$, δ) : 1.63 (3H, d, J=7.1Hz), 2.37 (3H, s),

2.46 (3H, s), 2.47 (3H, s), 4.27 (1H, d, J=17.2Hz), 4.50 (1H, d, J=17.2Hz), 5.53 (1H, s), 5.75-5.92 (1H, m), 6.60 (1H, s), 6.88-7.10 (6H, m), 7.22-7.50 (7H, m)

APCI-MASS (m/z) : 548 ($M+H^+$)

$[\alpha]_D^{30}$: -61.0° (C =1.02, $CHCl_3$)

(13) 1-[(R)-1-Phenylethyl]-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea

IR (KBr) : 3369, 3309, 2978, 2924, 1659, 1562, 1497, 1246, 1211 cm^{-1}

NMR ($CDCl_3$, δ) : 1.63 (3H, d, J=7.1Hz), 2.37 (3H, s), 2.46 (3H, s), 2.47 (3H, s), 4.27 (1H, d, J=17.2Hz), 4.50 (1H, d, J=17.2Hz), 5.53 (1H, s), 5.75-5.92 (1H, m), 6.60 (1H, s), 6.88-7.10 (6H, m), 7.22-7.50 (7H, m)

APCI-MASS (m/z) : 548 ($M+H^+$)

$[\alpha]_D^{29}$: +62.2° (C =1.02, $CHCl_3$)

(14) 1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(4-chloro-2-methylthio-6-methylpyridin-3-yl)urea

IR (KBr) : 3371, 3275, 3062, 2926, 2856, 1653, 1560, 1498 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.1 (12H, m), 2.44 (3H, s), 2.47 (3H, s), 4.25-4.45 (1H, m), 5.61 (2H, s), 6.89 (1H, s), 6.9-7.1 (6H, m), 7.37 (2H, d, J=8.6Hz)

APCI-MASS (m/z) : 530, 528 ($M+H^+$)

(15) 1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-(4-chloro-2-methylthio-6-methylpyridin-3-yl)urea

IR (KBr) : 3275, 3062, 3030, 2924, 1645, 1560, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 2.46 (3H, s), 2.49 (3H, s), 4.61 (2H, s), 4.63 (2H, s), 5.80 (1H, br s), 6.9-7.1 (7H, m), 7.25-7.4 (7H, m)

APCI-MASS (m/z) : 524, 522 ($M+H^+$)

(16) 1-Cycloheptyl-1-[4-(4-bromophenoxy)benzyl]-3-[2-chloro-4-methylthio-6-methylpyridin-3-yl]urea

mp : 105-107°C

IR (KBr) : 3379, 2926, 2854, 1668, 1579, 1483, 1238 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.08 (12H, m), 2.41 (3H, s), 2.48 (3H, s), 4.20-4.40 (1H, m), 4.54 (2H, s), 5.76 (1H, s), 6.82 (1H, s), 6.82-6.93 (2H, m), 6.95-7.08 (2H, m), 7.32-7.50 (4H, m)

APCI-MASS (m/z) : 588, 590, 592 ($M+H^+$)

(17) 1-Benzyl-1-[4-(4-bromophenoxy)benzyl]-3-[2-chloro-4-methylthio-6-methylpyridin-3-yl]urea

IR (KBr) : 3280, 3030, 2920, 1651, 1578, 1504, 1435, 1236, 804 cm^{-1}

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.49 (3H, s), 4.63 (2H, s), 4.64 (2H, s), 5.93 (1H, s), 6.84 (1H, s), 6.84-6.94 (2H, m), 6.94-7.07 (2H, m), 7.22-7.50 (9H, m)

APCI-MASS (m/z) : 582, 584, 586 ($M+H^+$)

(18) 1-Cycloheptyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2-chloro-4-methylthio-6-methylpyridin-3-yl]urea

mp : 165-166°C

IR (KBr) : 3205, 2926, 2856, 1624, 1572, 1491, 804 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30-1.90 (12H, m), 2.43 (6H, s), 4.00-4.18 (1H, m), 4.53 (2H, br s), 6.55-6.67 (1H, m), 7.12 (1H, s), 7.20-7.83 (5H, m), 8.11 (1H, br s), 12.85, 13.28 (total 1H, each br s)

APCI-MASS (m/z) : 484, 486 ($M+H^+$)

Example 29

The following compound can be obtained by treating 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-

methylpyridin-3-yl]urea with hydrochloric acid or hydrochloride in a conventional manner.

1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea·hydrochloride

Example 30

The following compound can be obtained by treating 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea with sulfuric acid in a conventional manner.

1-Benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea·sulfate

Example 31

The following compound was obtained according to a similar manner to that of Example 19.

1-Benzyl-1-[4-(4-fluorophenoxy)benzyl]-3-[2,4-bis(methylsulfonyl)-6-methylpyridin-3-yl]urea

IR (KBr) : 3348, 3066, 3030, 2927, 1734, 1668, 1610, 1583, 1497 cm^{-1}

NMR ($CDCl_3$, δ) : 2.67 (3H, s), 3.20 (3H, s), 3.32 (3H, s), 4.6-4.7 (4H, m), 6.9-7.1 (6H, m), 7.3-7.5 (2H, m), 7.62 (1H, br s), 7.88 (1H, s)

APCI-MASS (m/z) : 598 ($M+H^+$)

Example 32

The following compound was obtained according to a similar manner to that of Example 29.

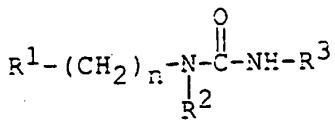
1-Cycloheptyl-1-[4-(4-fluorophenoxy)benzyl]-3-(2,4,6-trimethylpyridin-3-yl)urea hydrochloride

mp: 176-178°C

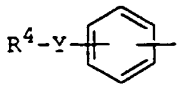
NMR (DMSO-d_6, δ) : 1.35-1.9 (12H, m), 2.32 (3H, s), 2.52(3H, s), 2.65 (3H, s), 4.1-4.3 (1H, m), 4.53 (2H, s), 6.95-7.4 (8H, m), 7.61 (1H, s), 8.30(1H, br s)

C L A I M S

1. A compound of the formula :



wherein
R^1 is a group of the formula :

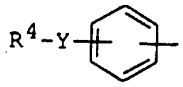


(in which
R^4 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and

Y is bond, lower alkylene, -S-, -O-, -C(=O)-, =CH-, -CONH-, -N(R^7)-CO-, (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2NH-$, $-SO_2NHCO-$ or $-CONHSO_2-$);
or
thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have suitable substituent(s);
R^2 is lower alkyl, lower alkoxy(lower)alkyl, cycloalkyl, ar(lower)alkyl which may have suitable substituent(s), heterocyclic group or heterocyclic(lower)alkyl,
R^3 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable

substituent(s), and
n is 0 or 1,
and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein
R^1 is a group of the formula :



(in which
R^4 is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen, lower alkyl, di(lower)alkylamino, protected amino, cyano, heterocyclic group which may have mono(or di or tri)-ar(lower)alkyl, hydroxy, protected hydroxy and mono(or di or tri)halo(lower)alkyl; or thienyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, pyrrolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl or methylenedioxyphenyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)ar(lower)alkyl and oxo;

Y is bond, lower alkylene, -S-, -O-, $-\overset{\overset{O}{\|}}{C}-$, =CH-, -CONH-, $-\underset{\underset{R^7}{|}}{N}-CO-$ (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2\dot{N}H-$, $-SO_2NHCO-$ or $-CONHSO_2-$); or
thiazolyl, imidazolyl, pyrazolyl, pyridyl,

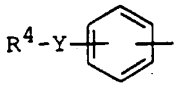
thienyl, furyl, isoxazolyl or chromanyl, each of which may have 1 to 5 substituent(s) selected from the group consisting of lower alkyl, hydroxy, protected hydroxy, phenyl, halophenyl, phenylthio and pyrrolyl;

R^2 is lower alkyl; lower alkoxy(lower)alkyl; cyclo(C_3-C_7)alkyl; phenyl(lower)alkyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen, lower alkoxy and di(lower alkyl)amino; tetrahydropyranyl; or furyl(lower)alkyl;

R^3 is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and halogen; pyridyl or pyrimidinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkylthio, halogen, lower alkoxy, lower alkylsulfinyl and lower alkylsulfonyl.

3. A compound of claim 2, wherein

R^1 is a group of the formula :



(in which

R^4 is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen, lower alkyl, di(lower)alkylamino, acylamino, cyano, tetrazolyl which may have mono(or di or tri)phenyl(lower)alkyl, hydroxy, lower alkoxy(lower)alkoxy and mono(or di or tri)halo(lower)alkyl; or thienyl, pyrazolyl, imidazolyl, triazolyl,

pyridyl, pyrrolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl or methylenedioxyphenyl, each of which may have one or two substituent(s) selected from the group consisting of lower alkyl, phenyl(lower)alkyl, triphenyl(lower)-alkyl and oxo;

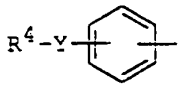
Y is bond, lower alkylene, -S-, -O-, $-\overset{\overset{O}{\|}}{C}-$, =CH-, -CONH-, $-\underset{\underset{R^7}{|}}{N}-CO-$ (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2NH-$, $-SO_2NHCO-$ or $-CONHSO_2-$); or

thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have 1 to 5 substituent(s) selected from the group consisting of lower alkyl, hydroxy, acyloxy, phenyl, halophenyl, phenylthio and pyrrolyl;

R^2 is lower alkyl; lower alkoxy(lower)alkyl; cyclo(C_3-C_7)alkyl; phenyl(lower)alkyl which may have one or two substituent(s) selected from the group consisting of halogen, lower alkoxy and di(lower alkyl)amino; tetrahydropyranyl; or furyl(lower)alkyl; and

R^3 is phenyl which may have two or three substituents selected from the group consisting of lower alkyl and halogen; pyridyl or pyrimidinyl, each of which may have two or three substituents selected from the group consisting of lower alkyl, lower alkylthio, halogen, lower alkoxy, lower alkylsulfinyl and lower alkylsulfonyl.

4. A compound of claim 3, wherein R^1 is a group of the formula :



(in which

R^4 is phenyl; halopheny; lower alkylphenyl; di(lower)alkylaminophenyl; lower alkylsulfonylaminophenyl; cyanophenyl; tetrazolylphenyl; (triphenyl(lower)-alkyltetrazolyl)phenyl; trihalo(lower)-alkylphenyl; phenyl having two lower alkyl and hydroxy; phenyl having two lower alkyl and lower alkoxy(lower)alkoxy; thienyl; pyrazolyl which may have lower alkyl or triphenyl(lower)alkyl; imidazolyl; triazolyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and phenyl(lower)alkyl; pyridyl; pyrrolyl; tetrazolyl which may have lower alkyl or triphenyl(lower)alkyl; oxazolyl; lower alkylthiazolyl; lower alkyloxa-diazolyl; lower alkylpiperazinyl; dioxothiazolidinyl; or methylenedioxyphenyl]; and

Y is bond, lower alkylene, -S-, -O-, -C(=O)-, =CH-, -CONH-, -N(R^7)-CO- (in which R^7 is lower alkyl), -NHSO$_2$-, -SO$_2$NH-, -SO$_2$NHCO- or -CONHSO$_2$-); halophenylthiazolyl; phenylimidazolyl; phenylpyrazolyl; phenylpyridyl;

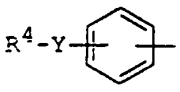
phenylthiopyridyl; pyrrolylpyridyl; phenylthienyl; phenylfuryl; phenylisoxazolyl; or chromanyl having 4 lower alkyl and hydroxy;

R^2 is lower alkyl, lower alkoxy(lower)alkyl, cyclo(C_3-C_7)alkyl, phenyl(lower)alkyl, halophenyl(lower)alkyl, lower alkoxyphenyl(lower)alkyl, di(lower alkyl)aminophenyl(lower)alkyl, tetrahydropyranyl or furyl(lower)alkyl, and

R^3 is pyridyl having two lower alkylthio and lower alkyl; pyridyl having halogen, lower alkyl and lower alkylthio; tri(lower alkyl)pyridyl; pyridyl having two lower alkoxy and lower alkyl; pyridyl having lower alkoxy, lower alkylthio and lower alkyl; pyridyl having two lower alkylsulfinyl and lower alkyl; pyridyl having two lower alkylsulfonyl and lower alkyl; pyridyl having lower alkylthio, lower alkoxy and lower alkyl; pyridyl having lower alkylsulfinyl, lower alkylsulfonyl and lower alkyl; pyridyl having lower alkylthio, lower alkylsulfonyl and lower alkyl; pyridyl having two halogen and lower alkyl; di(lower)alkoxypyrimidinyl; or pyrimidinyl having two lower alkylthio and lower alkyl.

5. A compound of claim 4, wherein

R^1 is a group of the formula :

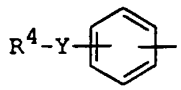


(in which R^4 is phenyl or halophenyl, and

Y is -O-),

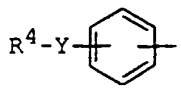
R^2 is cyclo(C_3-C_7)alkyl or phenyl(lower)alkyl,
R^3 is phenyl having two lower alkylthio and lower alkyl; tri(lower alkyl)pyridyl; pyridyl having two halogen and lower alkyl; pyridyl having halogen, lower alkyl and lower alkylthio; pyridyl having lower alkylthio, lower alkoxy and lower alkyl; pyridyl having lower alkylthio, lower alkylsulfonyl and lower alkyl; pyridyl having two lower alkylsulfonyl and lower alkyl; or pyrimidinyl having two lower alkylthio and lower alkyl; and
n is 1.

6. A compound of claim 5, wherein
R^1 is a group of the formula :



(in which R^4 is halophenyl, and
Y is -O-),
R^2 is cyclo(C_3-C_7)alkyl, and
R^3 is tri(lower alkyl)pyridyl; or
pyridyl having two lower alkylsulfonyl and lower alkyl.

7. A compound of claim 4, wherein
R^1 is a group of the formula :



(in which R^4 is pyrazolyl and
Y is bond),

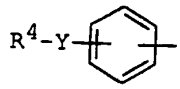
R^2 is phenyl(lower)alkyl, lower alkoxyphenyl(lower)alkyl, halophenyl(lower)alkyl, di(lower)alkylaminophenyl(lower)alkyl or cyclo(C_3-C_7)alkyl,

R^3 is pyridyl having two lower alkylthio and lower alkyl; pyridyl having halogen, lower alkyl and lower alkylthio; or pyrimidinyl having two lower alkylthio and lower alkyl; and

n is 1.

8. A compound of claim 7, wherein

R^1 is a group of the formula :



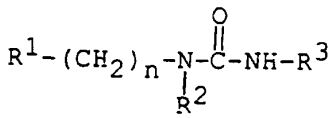
(in which R^4 is pyrazolyl, and

Y is bond),

R^2 is phenyl(lower)alkyl, and

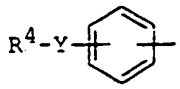
R^3 is pyridyl having two lower alkylthio and lower alkyl.

9. A process for preparing a compound of the formula :



wherein

R^1 is a group of the formula :



(in which

R^4 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and

Y is bond, lower alkylene, -S-, -O-, -C-, =CH-, -CONH-, -N-CO- (in which R^7 is lower alkyl), $-NHSO_2-$, $-SO_2NH-$, $-SO_2NHCO-$ or $-CONHSO_2-$); or

thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl, each of which may have suitable substituent(s);

R^2 is lower alkyl, lower alkoxy(lower)alkyl, cycloalkyl, ar(lower)alkyl which may have suitable substituent(s), heterocyclic group or heterocyclic(lower)alkyl,

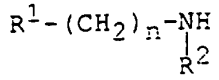
R^3 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and

n is 0 or 1,

or a salt thereof,

which comprises

(1) reacting a compound of the formula :



wherein R^1, R^2 and n are each as defined above, or a salt thereof with a compound of the formula :

$$O=C=N-R^3$$

wherein R^3 is as defined above, or a salt thereof to give a compound of the formula :

$$R^1-(CH_2)_n-N(R^2)-C(=O)-NH-R^3$$

wherein R^1, R^2, R^3 and n are each as defined above, or a salt thereof,

or

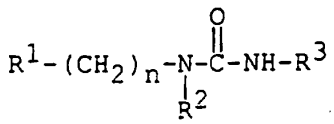
(2) subjecting a compound of the formula :

$$R^1-(CH_2)_n-NH(R^2)$$

wherein R^1, R^2 and n are each as defined above, or a salt thereof and a compound of the formula :

$$H_2N-R^3$$

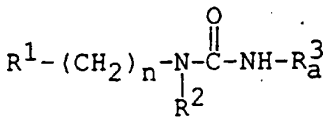
wherein R^3 is as defined above, or a salt thereof to formation of ureido group to give a compound of the formula :



wherein R^1, R^2, R^3 and n are each as defined above, or a salt thereof,

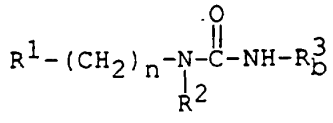
or

(3) subjecting a compound of the formula :



wherein R^1, R^2 and n are each as defined above, and R_a^3 is pyridyl having two lower alkylthio and lower alkyl,

or a salt thereof to oxidation reaction to give a compound of the formula :



wherein R^1, R^2 and n are each as defined above, and R_b^3 is pyridyl having two lower alkylsulfonyl

and lower alkyl; pyridyl having two lower alkylsulfinyl and lower alkyl; or pyridyl having lower alkylsulfonyl, lower alkylsulfinyl and lower alkyl; or a salt thereof.

10. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

11. A compound of claim 1 for use as a medicament.

12. A method of therapeutic treatment and/or prevention of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

13. Use of a compound of claim 1 for the manufacture of a medicament for treating and/or preventing hypercholesterolemia, hyperlipidemia, atherosclerosis of diseases caused thereby in human beings or animals.

INTERNATIONAL SEARCH REPORT

Internat A ation No
PCT/JP 95/01982

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C275/28 C07D213/75 C07D257/04 C07D231/12 C07D401/12
A61K31/17 A61K31/44 A61K31/41 C07D213/40 C07D307/38
C07D277/28 C07D233/54 C07C311/21 C07D333/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 623 662 (DE VRIES VERN G) 18 November 1986 cited in the application see column 9, line 9 - line 16; examples e.g. table 1, column 10, line 30 - line 35; see column 11 and 12, line 50 - line 60; claims 1-4 ---	1-3,12, 13
X	EP,A,0 399 422 (TAKEDA CHEMICAL INDUSTRIES LTD) 28 November 1990 see page 3, line 7 - line 13; claims 1,13,16; example 64 ---	1-3, 10-13
X	FR,A,2 661 676 (LIPHA) 8 November 1991 see claim 1; compound 8, 31, 76, 79 see page 18, line 30 - line 37 --- -/--	1-3,12, 13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 January 1996	-9. 02 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Seufert, G

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INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/JP 95/01982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 24458 (PFIZER ;HAMANAKA ERNEST S (US)) 9 December 1993 cited in the application see claims 1,9,10; examples 19,24	1-4,10, 12
X	PATENT ABSTRACTS OF JAPAN vol. 018 no. 575 (C-1268) ,4 November 1994 & JP,A,06 211814 (ONO PHARMACEUT CO LTD) 2 August 1994, see abstract	1-4
X	CHEMICAL ABSTRACTS, vol. 121, no. 25, 19 December 1994 Columbus, Ohio, US; abstract no. 292008, R. E. OLSON ET AL. see RN 159219-49-5 & BIORG. MED. CHEM. LETT., vol. 4, no. 18, 1994 pages 2229-2234,	1
X	EP,A,0 576 357 (SANOFI ELF) 29 December 1993 see claims 1,16; examples 180,190	1-3,10
X	DE,A,21 32 431 (RIEDEL DE HAEN AG) 11 January 1973 see page 17, first example	1-3
X	GB,A,1 598 900 (LILLY INDUSTRIES LTD) 23 September 1981 see claims 1,18; examples 59,62	1-3,10
A	US,A,5 169 844 (COMMONS THOMAS J ET AL) 8 December 1992 see column 1, line 8 - line 25; claims 1,21,22	1,5, 10-13
A	EP,A,0 370 740 (WELLCOME FOUND) 30 May 1990 see page 3, line 1 - line 24; claims 1,11-15; examples	1,10-13

2

INTERNATIONAL SEARCH REPORT

Int. ...al application No.
PCT/JP 95/01982

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched incompletely: 1-4,9-13
./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

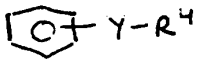
Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The definition of the substituents in claim 1 is too general and/or encompasses too broad a range of theoretically conceivable compounds so that a comprehensive search is not possible.
For economic reasons the search has been limited to the following cases (with regard to the disclosed examples):

R1 =  with R4 = aryl or heterocyclic group and Y as defined in claim 1

= -Cy1--Cy2 with Cy1 = thiazolyl, imidazolyl, pyrazolyl, pyridyl, thienyl, furyl, isoxazolyl or chromanyl as defined in claim 1, and Cy2 as carbo- or heterocyclic residue

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Ar ation No
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